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LOCAL AND SYSTEMIC REQUIREMENT OF GONADOTROPIN FOR LUTEINIZATION OF INTRAOCULAR OVARIAN TRANSPLANTS IN THE RABBIT

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THE REACTIONS of intraocular transplants of rabbit ovarian tissue to systemic hormonal stimulation have been reported by various workers. Allen and Priest found that, subsequent to intravenous administration of antuitrin, follutein, or human pregnancy urine, small vesicular follicles and blood-filled follicles appeared in such transplants. Sometimes large vesicular follicles developed and formed yellow-red corpora lutea. Lane and Markee obtained hemorrhagic follicles after administration of antuitrin S in most animals but "ovulation" in only 2 of the 20 rabbits used. May found intense vascularization and the development of 1 or more hemorrhagic follicles after intravenous administration of human pregnancy urine. Corpora lutea did not develop. All of these authors used autotransplants in castrated female rabbits. Ward, Gardner, and Newton (10, 11) used homotransplants in castrated and intact animals of both sexes and autotransplants in castrated and intact females. Intravenous administration of human pregnancy urine produced hyperemia followed by the development of vesicular and hemorrhagic follicles in viable transplants. Corpora lutea were not reported.

The rarity of a luteal reaction and the frequency of a hemorrhagic response are striking observations in the reports mentioned. Indeed, Ward, Gardner, and Newton (10) considered that the development of hemorrhagic follicles was a positive indication of gonadotropic action. The present report concerns a further study of the reactions of intraocular ovarian transplants to gonadotropins with a comparison of the systemic and local dosage required for luteinization of such transplants.

MATERIAL AND METHODS

Male and female rabbits, of the Dutch Belted line and 3 to 4 months of age, were used. Approximately one-eighth of an adult ovary,[1] in 3 to 5 fragments, was transplanted to each anterior chamber by the technique described elsewhere (2, 3, 12).

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[1]A few transplants were made of an entire fetal, or of half of a newborn, ovary.

TABLE I.—FOLLICULAR AND LUTEAL DEVELOPMENT IN OVARIAN TRANSPLANTS TO THE ANTERIOR CHAMBER OF THE RABBIT EYE UPON SYSTEMIC ADMINISTRATION OF HUMAN PREGNANCY URINE AND/OR PREGNANT MARE SERUM

		Ovarian transplant in left eye			*Ovarian transplant in right eye*		
			Development in relation to hormonal administration			*Development in relation to hormonal administration*	
Rabbit	*Hormone**	*Donor*	*Before*	*After*	*Donor*	*Before*	*After*
1. Female intact	PMS	N	No ff.	No change	N	No ff.	No change
2. Male intact	HPU	A	No ff.	No change	E	No ff.	No change
3. Female castrate	HPU, PMS	A	No ff.	No change	E	No ff.	No change
4. Female castrate	PMS	A	No ff.	No change	Nil		
5. Male castrate	PMS	A	No ff.	No change	Nil		
6. Male castrate	PMS	Nil			A	1 hf.	No change
7. Male castrate	HPU, PMS	A	5 ff.	2 corpora lutea	E	No ff.	No change
8. Female castrate	HPU	A	4 ff.	2 corpora lutea	E	No ff.	No change
9. Female castrate	PMS	A	3 hf.	1 new ff.; no change in the 3 hf.	A	4 ff.	2 corpora lutea
10. Female castrate	PMS	A	2 ff. 2 hf.	2 new ff.; 2 initial ff. became 2 hf; no change in initial 2 hf.	A	1 hf.	No change
11. Male castrate	PMS	A	1 ff.	1 corpus luteum; 1 new ff. which became a hf.	A	4 ff.	2 corpora lutea
12. Female castrate	PMS	A	2 ff. 1 hf.	2 ff. enlarged; no change in hf.	A	2 ff.	2 corpora lutea
13. Male intact	PMS	A	No ff.	2 ff.; 1 became a corpus luteum and 1 a hf.	A	1 ff.	1 corpus luteum

ff., vesicular follicle(s); hf., hemorrhagic follicle(s); E, 27 day fetus; N, newborn; A, adult.
*PMS—1,000 i.u. of gonadotropic hormone of pregnant mare serum as equal subcutaneous doses on 3 successive days.
HPU,PMS—200 i.u. PMS intraperitoneally, 5 c.c. of human pregnancy urine (2 month gestation) intravenously, and 450 i.u. PMS intravenously, each on 3 successive days.
HPU—20 c.c. of human pregnancy urine (3 month gestation) intravenously as equal doses on 2 successive days.

The majority of the intraocular transplants were autologous to castrated females, but occasionally homologous to both castrated and intact males. Most of the autotransplants in castrated females and the homotransplants in castrated males survived and showed continuous development of follicles over periods of at least 3 to 6 months (12). Small hemorrhagic follicles appeared occasionally; but corpora lutea never developed spontaneously.

Administration of the hormonal preparations was made between the second and fifth months after transplantation. For a comparison of the systemic with the local dosage only those animals with transplants showing vesicular follicles were used. Three types of gonadotropin-containing preparations were employed; human pregnancy urine (second or third month of gestation), gonadotropic hormone of pregnant mare serum and chorionic gonadotropin of pregnancy urine. The first two preparations were given intravenously, intraperitoneally, or subcutaneously. The third preparation was given intravenously for systemic action, and applied directly to the intraocular transplants for local action.

For intraocular application the dissolved hormonal preparation was mixed with a 2 per cent agar gel at 40 degrees C. in the proportion of 1 to 4. This mixture was immediately drawn into No. 16 trocars of the type used for the transplantation of the grafts. Rapid cooling produced a solid column of the mixture in the lumen of each trocar. The proportions of the mixture were such that each millimeter of the column contained 1.25 international units of chorionic gonadotropin. All but 3, 6, or 10 millimeters of the agar-gonadotropin columns in the trocars were then expelled. The re-

maining segments thus contained 3.75, 7.5, or 12.5 international units of gonadotropin. These segments, containing the desired dose levels,[2] were then introduced into the anterior chambers by the same procedure that was used for transplantation (Fig. 1). The segments were manipulated by blunt pressure on the cornea so as to lie in contact with the ovarian grafts (Fig. 2). Administration of these agar segments was made in one eye only. The segments remained intact within the anterior chambers indefinitely. In such administration the reaction of the transplant in the untreated eye was used to distinguish between local and systemic action of the agar-gonadotropin.

Animals were observed twice daily during the first week after the hormonal administration, daily in the second week, and thereafter once a week. Observations were made through a binocular dissecting microscope at magnifications ranging from 9 to 27 times. Diagrammatic sketches and color photographs of the grafts were made at the same intervals. Some animals were killed at various times for histologic preparations.

RESULTS

Systemic administration of pregnant mare serum and/or human pregnancy urine. The conditions governing the development of follicles and of corpora lutea were studied in 24 viable transplants in 13 animals (Table I). Two animals (Nos. 2 and 8) received human pregnancy urine only, 2 (Nos. 3 and 7) received human pregnancy urine and pregnant mare serum preparation, and the remaining 9 received pregnant mare serum preparation only.

In general transplants without vesicular follicles, and with or without hemorrhagic follicles, showed no response to gonadotropin administration. Transplants with vesicular follicles usually responded with luteinization of some or all of these follicles (Figs. 3 and 4).

Six transplants were derived from 27 day fetal or newborn donors (No. 1, both eyes; Nos. 2, 3, 7, and 8, right eyes). They had resided in the anterior chamber for approximately 2 months and, while well vascularized, they did not show follicles. Nor did they react in any visible way to gonadotropin administration.[3]

Six transplants of adult ovary, likewise well vascularized, did not have follicles at the time of gonadotropin administration (Nos. 1, 2, 3, 4, 5, and 13, left eyes). In only 1

[2] One animal (No. 37, Table III) received 15 i.u.

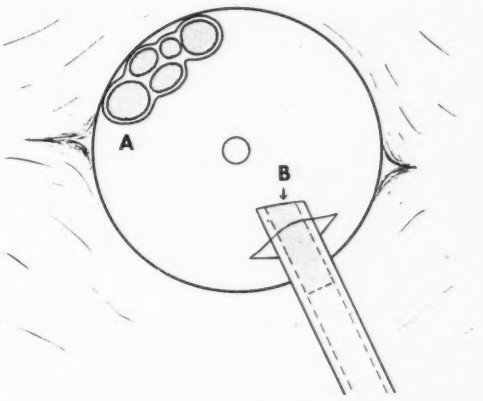

FIG. 1. Diagram of the introduction of agar-gonadotropin segment into the anterior chamber with an ovarian transplant. *A*, ovarian transplant; *B*, agar-gonadotropin.

[3] In these 6 transplants and 4 others derived from newborn donors, no follicular development occurred until 4 months after transfer into adult hosts.

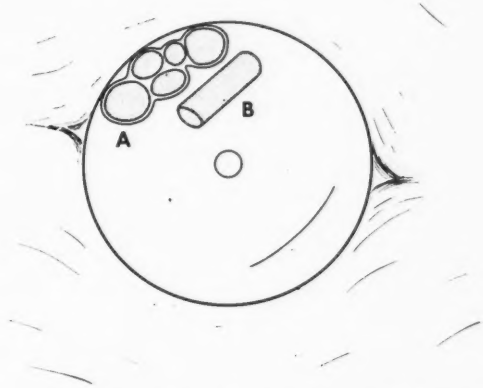

FIG. 2. Diagram of the agar-gonadotropin segment after being manipulated into position. Abbreviations as in Figure 1.

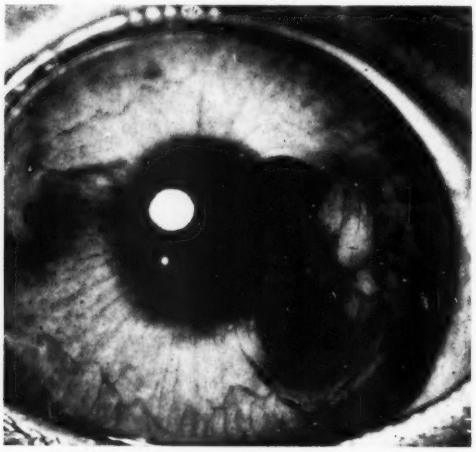

FIG. 3. Right eye of a castrated female Dutch Belted rabbit with an autologous ovarian transplant showing 2 vesicular follicles prior to gonadotropin administration.

(No. 13) was there any follicular response. In addition, 3 transplants showed only hemorrhagic follicles at the time of the gonadotropin administration (Nos. 6 and 10, right eyes; No. 9, left eye). Changes did not occur in these hemorrhagic follicles and a vesicular follicle appeared in only 1 transplant (No. 9, left eye).

In the remaining 9 transplants at least 1 vesicular follicle was present at the time of gonadotropin administration (Nos. 7 and 8, left eyes; No. 9, right eye; No. 10, left eye; Nos. 11 and 12, both eyes; No. 13, right eye). In 1 of these (No. 10, left eye) the 2 vesicular follicles became hemorrhagic and 2 new vesicular follicles appeared. In 1 other (No. 12, left eye) the 2 vesicular follicles enlarged to 3 times their original size. In the remaining 7 transplants 1 or more corpora lutea were formed from vesicular follicles; in 2 a new hemorrhagic follicle appeared.

When a luteal reaction resulted from gonadotropin administration the transplant became hyperemic within 8 hours. By the second to third day the vesicular follicles enlarged to 2 to 4 times their original size. By the fourth to fifth day free blood was visible in some or all of these follicles. This blood only partially filled the follicle concerned and accumulated at its lower pole. By the end of the fifth day the follicle lost its transparency, apparently because of multiplication of luteal cells and absorption of free blood. By the sixth day the follicle had become a reddish-yellow solid corpus luteum. Vascularization was usually by a single arborizing vessel whose main stem and lateral branches were engorged. Such corpora lutea remained unaltered for from 2 to 4 weeks. Their vascularity then diminished gradually with reduction in size leaving an opaque white mass.

Systemic and local administration of chorionic gonadotropin. For a comparison of the systemic and local actions of chorionic gonadotropin, only those transplants that showed at least 1 vesicular follicle (except in the right eye of No. 15, Table II) were used. All transplants were derived from adult donors; all hosts were castrated (5 males and 19 females, Tables II and III).

In intravenous administration, 1 of 7 transplants showed luteinization at 12.5 international units, 3 of 6 transplants at 25 international units, and 9 of 9 transplants at 50 or 100 international units, (Table II).

In local (intraocular in agar) administration none of 2 treated transplants showed luteinization at 3.75 international units, 1 of 5 treated transplants luteinized at 7.5 international units, and 5 of 5 treated transplants at 12.5 or 15 international units (Table III).

Systemic administration. Four animals, with 7 transplants, received 12.5 international units of chorionic gonadotropin intravenously. One transplant showed no reaction and 5 showed enlargement of existing vesicular follicles, appearance of new vesicular follicles, or development of a hemorrhagic follicle. In 1 transplant (No. 17, right eye) new vesicular follicles appeared and corpora lutea formed from the pre-existing ones.

Three animals, with 6 transplants, received 25 international units of chorionic gonadotropin intravenously. In 2 transplants (No. 20, both eyes) 4 corpora lutea

formed from 5 vesicular follicles. In 1 transplant (No. 19, left eye) 3 new vesicular follicles developed and, from the 4 follicles then present, 2 corpora lutea formed. Of the 3 remaining transplants, 1 did not show any reaction and 2 showed follicular enlargement with conversion of some vesicular follicles into hemorrhagic follicles.

Three animals, with 5 transplants, received 50 international units of chorionic gonadotropin intravenously (Nos. 21-23, Table II). All or most of the vesicular follicles in each transplant formed corpora lutea.

Two animals (Nos. 24 and 25, Table II), with 4 transplants, received 100 international units of chorionic gonadotropin intravenously. All vesicular follicles in all transplants formed corpora lutea.

Local administration. Twelve animals, having 23 intraocular transplants, received the agar preparation of chorionic gonadotropin in 1 eye only. Two of the 12 animals received 3.75 international units, 5 received 7.5 international units, 4 received 12.5 international units, and 1 received 15 international units (Table III).

The transplants in the treated and untreated eyes of the animals receiving 3.75 international units (Nos. 26 and 27) showed no changes.

Three of the 5 transplants in the treated eyes of those animals receiving 7.5 international units showed no changes or slight follicular enlargement (Nos. 28, 29, and 30); and 1 showed considerable follicular enlargement (No. 31). The transplants in the corresponding untreated eyes showed no changes (No. 30), formation of a hemorrhagic follicle (No. 29), or slight follicular enlargement (Nos. 28 and 31). In the remaining animal (No. 32) that received 7.5 international units the transplant in the treated eye formed 3 corpora lutea and 1 hemorrhagic follicle; the transplant in the untreated eye showed moderate follicular enlargement and the development of 1 additional vesicular follicle.

Corpora lutea formed in all 5 treated transplants in those animals receiving 12.5 or 15 international units (Nos. 33-37). In addition, 2 showed the formation of a hemorrhagic follicle (Nos. 34 and 35) and 1 an additional vesicular follicle (No. 36). No viable transplant was present in the untreated eye of 1 animal of the 5 (No. 33); in 3 of the remaining 4 untreated transplants there was either no change or slight follicular enlargement. In only 1 animal of the entire series (No. 36) was there any luteal reaction in the untreated transplant; here 1 corpus luteum formed and 1 additional follicle developed.

FIG. 4. Right eye of a castrated male Dutch Belted rabbit with a homologous ovarian transplant showing luteinization of 2 follicles and development of new vesicular follicles following gonadotropin administration.

DISCUSSION

Direct, in contrast to systemic, action has been shown for lactogenic hormone on the mammary gland, for testosterone and androsterone on the sparrow bill, and for progesterone on the endometrium. The systemic doses required to produce the same effect as the local dose was 75 times greater for lactogenic hormone, 8 times greater for testosterone or androsterone, and 25 times greater for progesterone.

In the present study the threshold dose of gonadotropin, when administered systemic-

TABLE II.—FOLLICULAR AND LUTEAL DEVELOPMENT IN OVARIAN TRANSPLANTS TO THE ANTERIOR CHAMBER OF THE RABBIT EYE UPON SYSTEMIC ADMINISTRATION OF HUMAN CHORIONIC GONADOTROPIN

		Ovarian transplant in left eye Development in relation to HCG administration		*Ovarian transplant in right eye Development in relation to HCG administration*	
Rabbit	*HCG administered*	*Before*	*After*	*Before*	*After*
14. Male castrate	12.5 i.u.	Nil		5 ff.	1 hf.; ff. enlarged
15. Female castrate	12.5 i.u.	1 ff.	1 ff. became a hf.; 1 new hf. formed	1 hf.	1 new hf.
16. Female castrate	12.5 i.u.	3 ff.	No change	3 ff.	ff. enlarged
17. Female castrate	12.5 i.u.	2 ff.	ff. enlarged; 1 new ff. formed	2 ff.	2 corpora lutea; 2 new ff. formed
18. Female castrate	25 i.u.	3 ff; 2 hf.	1 new hf.; ff. enlarged	2 ff.	ff. enlarged, became hf.
19. Male castrate	25 i.u.	1 ff.	ff. enlarged; 3 new ff. formed; 2 corpora lutea	1 ff.	No change
20. Male castrate	25 i.u.	2 ff.	2 corpora lutea	3 ff.	2 corpora lutea
21. Male castrate	50 i.u.	3 ff.	3 corpora lutea	Nil	
22. Female castrate	50 i.u.	3 ff.	3 corpora lutea	2 ff.	2 corpora lutea
23. Female castrate	50 i.u.	2 ff.	2 corpora lutea; 2 new ff. formed	3 ff.	1 corpus luteum
24. Female castrate	100 i.u.	3 ff.	3 corpora lutea	2 ff.;	1 new ff.; 3 corpora lutea
25. Female castrate	100 i.u.	2 ff.; 1 hf.	1 new ff.; 3 corpora lutea	2 ff.	2 corpora lutea

Abbreviations as in Table I.

ally, was 12.5 international units (1 of 7 transplants luteinized) while that of gonadotropin applied locally was 7.5 international units (1 of 5 transplants luteinized). Twenty-five international units systemically gave luteinization of half, and 50 international units of all of the transplants, while 12.5 international units locally gave luteinization of all treated transplants.[4] The ratio of the systemic to the local dose was between 2 to 1 and 4 to 1. However, in local application 1 transplant is exposed to the gonadotropin before the latter reaches the general circulation; in systemic administration each of the 2 transplants is exposed to the same circulating level. Consequently, the systemic dose required to produce the same effect on one transplant as the local dose may be only twice, or less than twice, the latter. The similarity of the effective systemic and local doses suggests a highly specific action of gonadotropin that is independent of a dilution factor.

Gonadotropins differ from sex steroids in having single, rather than multiple, target tissues. Even lactogenic hormone, assuming that it is identical with luteotropic hormone, acts upon both mammary gland and ovary. A minimal systemic dose of gonadotropin may still reach the follicles in effective amounts because it is not being metabolized throughout the organism; this dose may thus be of the same order as a local dose. The sex steroids and lactogenic hormone may need to reach a specific local concentration at the target organ when administered systemically. Consequently the dose of the hormone, when applied directly to the organ may be a fraction of that required systemically. Alternatively, the action of gonadotropins may be cumulative and that of the other hormones of the all-or-none type. That gonadotropins are selectively metabolized

[4]That the trauma involved in intraocular administration of agar-gonadotropin was not responsible for the luteal reaction is shown by the absence of such a reaction with doses less than 7.5 i.u. Walton and Hammond found that pricking vesicular follicles in rabbits did not affect them. Friedman (5) obtained no reaction from injection of saline into follicles in the rabbit ovary.

TABLE III.—FOLLICULAR AND LUTEAL DEVELOPMENT IN OVARIAN TRANSPLANTS TO THE ANTERIOR CHAMBER OF THE RABBIT EYE UPON LOCAL ADMINISTRATION OF HUMAN CHORIONIC GONADOTROPIN TO ONE TRANSPLANT

		Development of ovarian transplants in relation to HCG administration			
		Eye with HCG		*Eye without HCG*	
Rabbit	*Dosage of HCG*	*Before*	*After*	*Before*	*After*
26. Female castrate	3.75 i.u.	5 ff.	No change	8 ff.	No change
27. Female castrate	3.75 i.u.	5 ff.	No change	4 ff.	No change
28. Female castrate	7.5 i.u.	2 ff.	No change	4 ff.	Slight enlargement of ff.
29. Female castrate	7.5 i.u.	5 ff.	No change	2 ff.	1 hf.
30. Female castrate	7.5 i.u.	6 ff.	Slight enlargement of ff.	5 ff.	No change
31. Female castrate	7.5 i.u.	2 ff.	ff. enlarged to 3× original size	2 ff.	Slight enlargement of ff.
32. Female castrate	7.5 i.u.	9 ff.	3 corpora lutea; 1 hf.	2 ff.	ff. enlarged to 2× original size; 1 new ff.
33. Female castrate	12.5 i.u.	4 ff.	3 corpora lutea	Nil	
34. Male castrate	12.5 i.u.	7 ff.	4 corpora lutea; 1 hf.	3 ff.; 1 hf.	No change
35. Female castrate	12.5 i.u.	2 ff.	3 corpora lutea; 1 hf.	1 ff.	Slight enlargement of ff.
36. Female castrate	12.5 i.u.	2 ff.	2 corpora lutea; 1 new ff.	1 ff.	1 corpus luteum; 1 new ff.
37. Female castrate	15 i.u.	2 ff.	1 corpus luteum	2 ff.	No change

Abbreviations as in Table I.

by ovarian tissue is suggested by the lack of growth or follicular activity of ovarian transplants in intact female rats or mice. Pituitary gonadotropins stimulate the intact ovaries but, apparently, none are available for the additional tissue of the transplant although the latter will grow and function upon castration of the host.

However, in the agar technique of local administration, it is not known how much, or for how long, gonadotropin remains in the anterior chamber.[5] The anterior chamber is reputed to have almost direct drainage into the venous system of the eye. The large iridial area, with its capilliary bed, offers a very extensive secretory and absorbtive surface. Anterior chamber fluid lost in intraocular transplantation is reconstituted within 6 hours.

Friedman (5) obtained luteinization of follicles in one ovary of 18 of 22 intact rabbits by their direct irrigation with extracts of pregnancy urine. In only 1 animal did luteinization occur in the other (untreated) ovary. However, he found that the corpora lutea began to regress after the eleventh day unlike those in pseudopregnant animals. In the present study many, though not all, of the induced corpora lutea began to regress at a similar time.

The frequency of a hemorrhagic, rather than a luteal, reaction in intraocular ovarian transplants following the administration of chorionic gonadotropin has already been noted in the work of others. In transplants of rabbit ovaries to the rectus sheath Friedman (4) found hemorrhagic follicles as a postcoital reaction. In 9 animals with viable transplants 7 showed blood-filled follicles and 2 developed corpora lutea. Walton and Hammond also noted frequent hemorrhagic follicles in the ovaries of intact animals following coitus.

In the present study hemorrhagic fol-

[5]Solutions of trypan blue injected into the anterior chamber color the fluid for several hours; agar gel containing microcrystalline testosterone phenylacetate in the anterior chambers of mouse eyes retained appreciable amounts of this hormone for 2 months.

licles occurred at random in both treated and untreated hosts (Tables I, II, and III). The dosages of gonadotropin in treated animals were usually 1,000 international units of equine gonadotropin and from 3 to 100 international units of human chorionic gonadotropin. Lloyd found that 600 international units of equine gonadotropin gave follicular development (but no luteinization) in the intact ovaries of immature rabbits. She did not mention hemorrhagic follicles. Lane and Markee, using intraocular transplants in castrated females, found hemorrhagic follicles an almost ubiquitous reaction to 20 international units of antuitrin S. Ward, Gardner, and Newton (10) stated that hemorrhagic follicles in intraocular grafts could be produced by "as little as 60 international units of chorionic gonadotropin per kilogram of animal weight" but that, in some animals, even 150 international units per kilogram resulted in hyperemia only. Most of the animals used by these authors were of the New Zealand line, presumably with weights of 3 to 4 kilograms and therefore receiving 180 to 240 international units of chorionic gonadotropin. This dosage is approximately 10 times that required systemically for a luteal reaction in transplants in Dutch Belted rabbits whose weights ranged from 1.5 to 2.25 kilograms. Actually, Ward, Gardner and Newton (10) mention a dosage of 500 international units of chorionic gonadotropin as that which "would normally produce an almost 100 per cent response." Strain differences in reactivity to hormones do exist (e.g., estrogen sensitivity in inbred mouse strains). However, the statement of Ward, Gardner and Newton (10, 11) that their transplants were not mature histologically, their use of tissue from animals ranging in age from newborn to 12 weeks, and their inference that follicles were only detectable histologically make evaluation difficult. In the present study, the development of follicles and corpora lutea as a response to gonadotropic stimulation occurred only once in a transplant not showing vesicular follicles initially (Table I, No. 13). Only those transplants that already showed follicles were employed for evaluation of systemic and local reaction to gonadotropin.

Friedman (4) considered that hemorrhagic follicles occurred normally in unmated rabbits through degeneration of vesicular follicles and that the high incidence in his transplants was abnormal and related to the coital stimulus. Lane and Markee considered that such follicles occurred as a reaction to exogenous gonadotropin because the vesicular follicles in their transplants had passed the optimal size. Zondek found that the formation of hemorrhagic follicles was the most constant reaction to administration of gonadotropins in the immature mouse ovary. Such follicles occurred characteristically in intraocular ovarian transplants in castrated male mice without exogenous hormonal administration and in similar transplants in castrated and intact male and castrated female mice treated with estrogen, testosterone, or progesterone. They also appeared in intraocular transplants in untreated castrated female mice when the transplants were of very small size. The same type of blood-filled follicle also appeared in intrasplenic ovarian grafts in castrated male and female mice and guinea pigs. Such follicles apparently occur in general when there is an alteration of the normal gonadotropin-ovarian hormonal balance.

SUMMARY

1. Thirty-seven Dutch Belted rabbits received intraocular transplants of ovarian tissue. Most of the transplants were autologous in castrated females although a few were homologous in castrated and intact males. Almost all animals received transplants in both eyes.

2. Thirteen animals received between 650 and 1,000 international units of equine gonadotropin and/or from 5 to 20 cubic centimeters of human pregnancy urine. Transplants that did not have vesicular

follicles did not react. Transplants with such follicles showed enlargement of existing follicles, development of new follicles, or formation of corpora lutea.

3. Twelve animals, with transplants having vesicular follicles, received a single intravenous administration of chorionic gonadotropin. Follicular luteinization at 12.5 international units was rare, occurred in half the transplants at 25 international units, and in all transplants at 50 or 100 international units.

4. Eleven animals, with transplants with vesicular follicles in both eyes, received chorionic gonadotropin in an agar block in one eye only. Follicular luteinization in the treated eye did not occur at 3.75 international units, was rare at 7.5 international units, and occurred in all cases at 12.5 and 15 international units. The transplant in the untreated eye of only 1 animal luteinized (at 12.5 i.u.). One other rabbit, with a transplant in the treated eye only, received 12.5 international units with consequent luteinization.

5. Hemorrhagic follicles occurred apparently at random in both treated and untreated animals.

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STUDIES TO DETECT THE ESCAPE OF AMNIOTIC FLUID INTO THE MATERNAL CIRCULATION DURING PARTURITION

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SINCE ITS CLASSIC DESCRIPTION by Steiner and Lushbaugh in 1941 the pathogenesis, diagnosis, and clinical management of amniotic fluid embolism has become of increasing interest and importance to the obstetrician-gynecologist. Characteristically, this syndrome occurs in parous women in whom there is rupture of the amniotic sac associated with very forceful uterine contractions. Amniotic fluid with its particulate matter consisting of fetal squamous epithelial cells, hairs, and vernix presumably enters the maternal circulation through incomplete uterine or cervical lacerations or at the site of placental implantation following some degree of separation. In some instances, the clinical manifestations are unconsciousness, convulsions, cyanosis, and severe shock followed rapidly by death. In other instances, cardiopulmonary complications may be less intense initially, and death does not immediately result. Instead, massive hemorrhage from the genital tract, from the operative field, or from any site of trauma heralds the development of hypofibrinogenemia and probably other abnormalities in the hemostatic mechanism as described by Ratnoff and Vosburgh.

A third complication of the escape of amniotic fluid into the maternal circulation but one which would manifest itself much later has been suggested by Muirhead and Montgomery. Stimulated by the finding of primary pulmonary hypertension with pulmonary arterial and arteriolar sclerosis in a young woman who had been pregnant recently, they studied the effects of small amounts of human amniotic fluid injected intravenously on the pulmonary vessels of rabbits. Widespread lesions developed in the small pulmonary arteries characterized by fibrosis or hyalinization of the arterial wall and endarteritis obliterans. They postulated that subclinical amniotic fluid embolism may occur during labor and delivery, and subsequently pulmonary vascular sclerosis could develop as the result of this foreign material being entrapped within these vessels (1, 2).

Repeated mention has been made of the possible etiologic role played by pitocin in the production of amniotic fluid embolism when the drug is used to initiate and maintain labor. However, attempts to implicate pitocin on the basis of its use in some cases in which amniotic fluid embolism occurred must be interpreted in terms of the relative frequency with which pitocin is used in the areas from which these reports came.

During the past 2 years in the city of Dallas there have been 2 proved cases of amniotic fluid embolism. In 1, the patient expired almost immediately after the first sign of distress. In the other, death did not occur until 4¼ hours after the initial evidence of difficulty and defective blood coagulation was demonstrated.

CASE 1. D. H. was 27 years old, pregnant for the second time, and at term. Her prenatal course had been uneventful. She was admitted to the hospital with irregular mild uterine contractions. Amniotomy was attempted but fluid was not observed to escape subsequently. An infusion of diluted pitocin was given intravenously for 4 hours without the establishment of true labor. The patient was discharged.

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Two days after her previous admission, she reentered the hospital in hard labor. The patient had noted no fetal movement that morning and fetal heart tones were not heard. At 11:30, 15 minutes after admission, demerol and scopolamine were given. The patient vomited once but there was no evidence of aspiration. At 12:00 the vertex was at plus 2 station and the cervix was dilated to 9 centimeters. While the patient was being transferred to the delivery room she convulsed and became cyanotic. An airway was established through clenched teeth and the patient gasped a few times. Tracheal intubation was performed and the upper respiratory tract was found to be clear. No heart beat or respirations were detected after this. She was pronounced dead at 12:05.

Histologic study revealed squames, mucin, and numerous polymorphonuclear cells in the arterioles of the lungs, the veins of the uterus and ovaries, and the portal vessels of the liver. The site of entry of the amniotic fluid into the maternal circulation was not detected.

CASE 2. M. K., a 36 year old, gravida 4, para 3, was admitted to the hospital at 3:45 in early labor. Her prenatal course had been uneventful. At 6:30 the patient was having painful uterine contractions so that 100 milligrams of demerol were given. The cervix was 3 to 4 centimeters dilated, and the occiput was at a minus 2 station. The membranes were not known to be ruptured. At 7:30, after 1 hour of hard contractions, the patient suddenly became dyspneic, cyanotic, and then unconscious. At 7:40 the blood pressure and pulse were unobtainable; fetal heart tones ceased.

At 8:00 blood drawn from a peripheral vein for clot observation was subsequently noted on smear to contain amniotic fluid particulate matter. This blood formed only a very small clot. At 8:15 numerous hematomas as well as bleeding from the several venipuncture sites were noted. At 8:45, at the time of delivery of a stillborn 8 pound 2 ounce infant, rales were noted in the left lung. In spite of therapy with oxygen given by intermittent positive pressure, whole blood, and fibrinogen the patient's status continued to deteriorate and she expired at 11:47.

Histologic study of the organs obtained at necropsy revealed extensive pulmonary edema and the classic picture of fetal squames, lanugo hairs, and mucin in small pulmonary arteries and arterioles (Fig. 1).

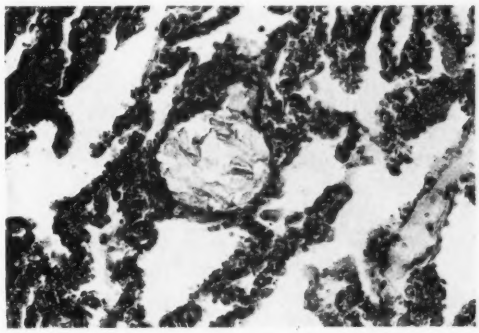

FIG. 1. This photomicrograph of lung from Case 2 shows many amniotic fluid squames in a small pulmonary artery.

This report concerns studies designed primarily to answer the following questions: (1) Do slight to moderate amounts of amniotic fluid regularly or even occasionally escape into the maternal circulation during labor or delivery without producing clinical evidence of such an escape? (2) Is the detection of any amniotic fluid debris in maternal blood vessels always an indication of a pathologic state or can it represent a normal event regularly associated with labor and delivery? (3) Does the use of pitocin to initiate and maintain labor enhance the escape of amniotic fluid into the maternal circulation?

AMNIOTIC FLUID LABELLING

To demonstrate any transfer of amniotic fluid into the maternal circulation a readily identified label for the amniotic fluid is essential. In fatal cases the accepted evidence for such a transfer is the histologic finding of fetal squames and lanugo hairs in the pulmonary vasculature. Differing from the second case reported typically amniotic fluid debris is not identified in the peripheral blood. Therefore, a search for such particulate material in the peripheral blood usually would be of little value for detecting the transfer of amniotic fluid into the uterine venous system.

The possibility that maternal red blood cells labelled with radioactive sodium chromate ($Na_2Cr^{51}O_4$) and placed in the amniotic sac might prove a satisfactory "tag" to detect any transfer of amniotic fluid into the maternal circulation was considered. Erythrocytes so labelled seemed most suitable since their size approximates that of fetal squames yet, of course, they would be small enough to pass through the pulmonary vas-

cular tree into the peripheral blood where they could be readily identified. Furthermore, they probably would not be treated as foreign material by the body defense mechanisms and would not be rapidly sequestered or destroyed.

Preliminary studies in which red cells were added to sterile amniotic fluid in vitro and incubated at 37 degrees C. for 24 hours revealed that amniotic fluid was no more than slightly hemolytic. Subsequent studies performed in vivo also yielded only minimal evidence of hemolysis within the amniotic fluid at the end of 24 to 36 hours. In 5 instances in which it was measured, the radioactivity free in the amniotic fluid 24 hours after tagging was less than 10 per cent of the total amniotic fluid radioactivity and the amniotic fluid supernatant after centrifugation contained no visible hemoglobin.

Thirty to 50 milliliters of blood drawn from the mother were incubated with 150 to 200 microcuries of $Na_2Cr^{51}O_4$ in acid-citrate-dextrose (ACD) solution for 20 to 40 minutes at room temperature with occasional agitation of the flask. The supernatant liquid was removed after centrifuging, and the separation was repeated after resuspending the red cells in 3 to 4 times their volume of isotonic saline solution. After 2 such washings enough saline was added to restore or slightly exceed the original volume of blood. At this time 98 to 100 per cent of the radioactivity was bound to the erythrocytes.

A carefully measured volume ranging from 20 to 40 milliliters of a suspension of red cells so labelled and suspended in saline and containing about 100 microcuries of radioactive chromium was introduced transabdominally into the amniotic sac to effect tagging of the amniotic fluid. To accomplish this, local infiltration from the skin to the peritoneum with 1 per cent procaine was carried out. Then amniocentesis was performed with a 16 gauge steel needle ordinarily used for caudal analgesia and the cell suspension was injected into the amniotic sac. Leakage into the peritoneal cavity was prevented by firm pressure over the injection site for 10 minutes. Fetal heart tones were checked repeatedly throughout the procedure and for 2 to 4 hours thereafter. No irregularities were noted.

The possibility existed that, while the red cells would not be lysed in the amniotic fluid, they would be considerably altered by it. Therefore, even though they were transferred to the maternal circulation, they might be rapidly removed from the circulation and destroyed. To rule out this possibility 2 studies were performed. Amniotic fluid tagged with the patient's labelled red cells 24 hours before was obtained aseptically at the time of cesarean section. Then 8.0 milliliters of this were injected intravenously into a patient of the same blood type with terminal ovarian carcinoma, and the resultant circulating erythrocyte radioactivity was determined 1 hour later. In another instance the amniotic fluid was similarly tagged. At the time of cesarean section all of it was collected aseptically, and 100 milliliters of the tagged amniotic fluid were placed free in the peritoneal cavity of the same patient. Then the peripheral blood was checked during the next 7 days for evidence of erythrocyte radioactivity.

MEASUREMENTS TO DETECT ANY TRANSFER

The patients selected for study were either for repeat cesarean section (13 patients) or were at term and were either in very early labor or were suitable for induction of labor (25 patients). From 2 to 24 hours after tagging the amniotic fluid, spontaneous labor with delivery occurred in 13 and labor was induced and maintained with dilute intravenous pitocin solution in 12.

Maternal blood specimens were collected before cesarean section or at the start of induction of labor, when the amniotic sac ruptured, at delivery, and every 24 to 48 hours thereafter for 2 to 5 days. Amniotic fluid was collected at the time of delivery when cesarean section was performed and at the time of rupture of the membranes and again at delivery when vaginal delivery was performed. Cord blood was collected at de-

livery, and blood was also drawn from the infant each 24 to 48 hours for 2 to 5 days thereafter. The hematocrit of each blood specimen was determined. The specimens were then counted in a well-type scintillation counter.

The approximate volume of circulating red cells was calculated from the plasma volume measured with Evans blue dye and the hematocrit in 6 instances. In the remainder of the cases, merely assuming that the subject's blood volume was about 4,000 to 5,000 milliliters depending upon body size proved satisfactory for this study.

The apparent volume of amniotic fluid transferred to the maternal circulation was calculated as follows:

$$\text{Volume transferred} = \frac{\text{Radioactivity per ml. of red cells} \times \text{total red cell volume}}{\text{Radioactivity per ml. of amniotic fluid}}$$

RESULTS

No deleterious effects were noted when the small volume of amniotic fluid which had been tagged with compatible red cells 24 hours before was injected intravenously into a recipient with terminal carcinoma. One hour later the circulating radioactivity equalled the value which theoretically should have resulted from its mixing with the total volume of blood present in the recipient.

When amniotic fluid tagged the day before with labelled erythrocytes was collected at the time of cesarean section and then placed free in the subject's peritoneal cavity, labelled red cells promptly appeared in the maternal circulation and reached a maximum concentration on the fourth day. At this time the erythrocyte radioactivity accounted for 66 per cent of that originally placed in the peritoneal cavity. The erythrocyte radioactivity persisted for at least 7 days.

Radioactivity in the maternal blood at the time of rupture of membranes, at delivery, and postpartum in the 3 groups ranged from none to a barely detectable level. Actually, it was never significantly greater than background activity. If it were assumed that the differences from background activity were real, the total circulating maternal red cell activity was equivalent to that in 1.2 milliliters of amniotic fluid in the group which was delivered by cesarean section without labor, 1.8 milliliters in those who underwent spontaneous labor and vaginal delivery, and 1.0 milliliter in the group in which labor was induced and maintained with pitocin. The greatest individual value was 6.5 milliliters in a subject with intact membranes delivered by cesarean section.

Fetal blood activity was somewhat higher than that in maternal blood and was almost totally in the plasma. It was noted, in general, that the longer the interval between the tagging of the amniotic fluid and delivery, the higher the fetal plasma activity, but even after an interval of 30 hours the fetal activity was still quite low. The finding of higher radioactivity in fetal blood than in maternal blood suggested swallowing of labelled material by the fetus. This has been substantiated. The observations made will be reported.

These studies did not cause any apparent maternal or fetal morbidity.

DISCUSSION

The technique of tagging amniotic fluid with maternal red cells labelled with radioactive chromium for the purpose of detecting any transfer of amniotic fluid into the maternal circulation appears to be a valid one. Its validity depends upon whether or not red cells so treated and then transferred to the mother will circulate in the maternal blood stream for a reasonable period of time without being either rapidly sequestered or hemolyzed. Observations in 1 instance in which compatible red cells in a small volume of amniotic fluid were given intravenously indicate that rapid sequestration or hemolysis did not occur. Furthermore, when amniotic fluid tagged 24 hours before with labelled red cells was placed free in the peritoneal cavity, radioactive red cells promptly appeared in the maternal blood and re-

mained there for several days. From the studies of Pritchard, Weisman, and Adams (5, 6) it can be concluded that this resulted from the transfer of intact labelled erythrocytes from the peritoneal cavity into the intravascular compartment and not simply from the transfer of only radioactive chromium released from lysed erythrocytes. They have shown that the placement of either labelled and then hemolyzed red cells or intact but grossly incompatible labelled erythrocytes into the peritoneal cavity does not result in circulating erythrocyte radioactivity. However, when compatible labelled cells are introduced into the peritoneal cavity an average of two-thirds of the radioactivity subsequently is found in the circulating red cells.

To have encountered a massive transfer of amniotic fluid into the maternal circulation with the resultant clinical picture of amniotic fluid embolism during this study would have been exceedingly unlikely because of the apparent rarity of such an event. However, in none of 25 subjects in whom there was labor, rupture of membranes, and vaginal delivery was there any evidence of more than a trace amount of amniotic fluid entering the maternal circulation. Consequently, it would not seem justified to assume that either clinically evident or histologically proved amniotic fluid embolism results from an intensification of a process which occurs frequently but to a lesser degree during labor or delivery. Therefore, the histologic identification of squames or other amniotic fluid debris in the vessels of maternal lungs is indicative of a pathologic process. Although trophoblastic cells can be transported to pulmonary vessels commonly during labor and delivery, the identification of any amniotic fluid debris at this site cannot be considered normal.

It has been implied in several clinical reports that the use of pitocin to stimulate and maintain labor is more likely than is spontaneous labor to result in the escape of amniotic fluid into the maternal circulation or to enhance the possibility of defibrination by intravascular coagulation. Neither the observations in this study nor those made by Pritchard support this implication (3, 4).

SUMMARY AND CONCLUSIONS

Maternal erythrocytes labelled with $Na_2Cr^{51}O_4$ were introduced transabdominally into the amniotic sac prior to labor and delivery to serve as a "tag," and then the maternal blood was checked for the appearance of radioactivity during and after labor and delivery. Appropriate studies were performed to assure the validity of this technique for measuring any transfer of amniotic fluid into the maternal circulation.

It is concluded on the basis of these studies that normally practically no amniotic fluid escapes into the maternal circulation during labor or delivery, that the use of pitocin to initiate and maintain labor does not especially enhance its escape, and that the finding of any amniotic fluid debris in the maternal lungs is evidence of a pathologic process rather than merely an aftermath of normal labor and delivery.

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ANERGY AND SKIN HOMOGRAFT SURVIVAL IN HODGKIN'S DISEASE

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THE EVIDENCE at present strongly supports the view that the rejection of homografts in man and other species is brought about by an immunologic response. The type of response involved most closely resembles the phenomenon known as delayed, bacterial-type hypersensitivity. The evidence for this view has been recently reviewed by Lawrence. A familiar example of delayed hypersensitivity is the Mantoux test for tuberculosis.

It has long been known that Hodgkin's disease is associated with an increased susceptibility to infection with tuberculosis as well as various bacterial and fungus diseases. This has been attributed in part to the presence of anergy to tuberculin observed in many of the patients in whom proved tuberculosis coexists with Hodgkin's disease. Recently Schier and associates (6, 7) studied a group of patients suffering from Hodgkin's disease. Using a battery of skin tests to antigen solutions of bacterial, fungus, and viral origin commonly encountered in everyday life, they demonstrated that cutaneous unresponsiveness is present in a high percentage of patients with Hodgkin's disease. Whether this is a primary or secondary feature of the disease remains to be determined. Granted that this observation was correct, then this situation would represent another so-called "experiment of nature," as termed by McQuarrie, and afford an opportunity to define the role of delayed bacterial hypersensitivity in homograft rejection in man. Further than this, the question of a primary immunologic defect in Hodgkin's disease is raised which could lead to a new understanding of this puzzling disease and conceivably open the door to new therapeutic approaches to this serious affliction.

It thus seemed pertinent to repeat Schier's observations and to extend them by performing homografts of skin in patients with Hodgkin's disease. The preliminary results of this work are reported herein.

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MATERIALS AND METHODS

Skin tests for delayed bacterial hypersensitivity. Two groups of patients were studied. The first group consisted of 28 patients with Hodgkin's disease. The diagnosis was based upon histologic evidence in each case. All but 1 of the patients were ambulatory at the time of testing. The 1 exception was a bedridden elderly individual who, however, was not moribund. Three of the patients were female children aged 12, 13, and 13 years respectively. Ages in the adult group ranged from 20 to 69 years, the average being 38 years. All the adult patients were male. Although many of the patients had received treatment for the disease in the past, skin testing was carried out in most instances at the beginning of a new admission prior to treatment. In a few instances skin testing was carried out following treatment with cortisone or nitrogen mustard. In such cases, a minimum interval of 1 week was allowed to elapse following conclusion of treatment before proceeding with the tests. In a number of the patients, only local irradiation to cervical lymph nodes had been given prior to skin testing. The second group consisted

TABLE I.—THE INCIDENCE OF POSITIVE SKIN REACTIONS AT 24 AND 48 HOURS IN RESPONSE TO A VARIETY OF COMMON MICROBIAL ANTIGENS

	Patients with Hodgkin's disease (28)		*Patients without Hodgkin's disease (208)*	
	No.	*Per cent*	*No.*	*Per cent*
Schick control	2	7	21	10
SK-SD	6	21	138	66
Mumps	7	25	182	88
Mumps control	0	0	7	3
Trichophyton	6	21	126	61
Candida	2	7	119	57
P.P.D.	4	14	108	52

TABLE II.—FREQUENCY DISTRIBUTION OF THE POSITIVE SKIN REACTIONS AT 24 AND 48 HOURS IN RESPONSE TO A VARIETY OF COMMON MICROBIAL ANTIGENS

No. of positive responses	*Hodgkin's —patients (28)—*		*Non-Hodgkin's —patients (208)—*	
	No.	*Per cent*	*No.*	*Per cent*
0	18	64	3	1
1	2	7	8	4
2	5	18	41	20
3	1	4	59	28
4	1	4	60	29
5	1	4	30	15
6	0		5	2
7	0		2	1

of 208 hospitalized patients suffering from a wide variety of diseases. Individuals with other varieties of lymphoma and patients with terminal carcinoma were excluded from this group. Testing was not done in patients who were critically ill. Indeed, all patients included were ambulatory at the time of testing. Patients receiving steroid therapy or nitrogen mustard and related compounds were not tested. All of the subjects in this group were male. The ages ranged from 21 to 81 years with an average of 44 years.

The materials used for skin testing were solutions or suspensions of the following antigens:

1. Diphtheria toxoid (Shick control solution) containing .008 Lf dose of diphtheria toxoid per 0.1 cubic centimeter obtained from the Department of Public Health, Massachusetts Public Health Biologic Laboratories, Boston, Massachusetts.
2. Streptokinase—streptodornase (10 units SK and 2.5 units SD per 0.1 c.c. powdered varidase was appropriately diluted prior to the beginning of the study.)
3. Mumps skin test antigen.
4. Mumps skin test control solution.
5. Trichophyton gypseum extract in a 1:30 dilution of the full strength antigen.
6. Candida albicans extract in a 1:100 dilution of the full strength antigen.
7. Purified protein derivative (P.P.D.) intermediate strength containing 0.0001 milligram P.P.D. per 0.1 cubic centimeter.

Tests were performed in the conventional manner by the injection of 0.1 milliliter of each antigen intradermally into the skin of the forearms. The injection sites were marked and readings were made at 5 minutes and 24 and 48 hours following injection. The development of edema and erythema was noted and recorded by measuring 2 diameters at right angles on the respective areas of reaction. For the purposes of this article the responses are reported simply as positive or negative. A positive reaction is recorded when induration is present and the diameter of the area of induration and erythema is at least 5 millimeters. In the majority of instances, in positive reactions the diameter of the induration measured greater than 10 millimeters.

Homografting of skin. Skin homografts were carried out in 13 of the patients with Hodgkin's disease previously skin tested as described. Ten of these patients were adult males and 3 were female children. Selection of the patients was influenced chiefly by willingness to participate in the study on a voluntary basis and the anticipated ease of prolonged follow-up study. Under local anesthesia with procaine, a full thickness diamond-shaped piece of skin measuring 1.5 by 2.0 centimeters was excised from the selected site (usually the anteromedial aspect of the thigh), and a full thickness homograft of the same dimensions was sutured in place with interrupted stitches of fine silk. For purposes of identification, the grafts were tattooed with India ink making a regular pattern of spaced dots. Bacitracin ointment was applied to the edges of the wound and a stent dressing was utilized. The dressing and stitches were removed at 8 to 10 days following which the graft was left exposed to the air. The status of the graft was deter-

mined by simple inspection and palpation along with frequent photographic recording. Observations were carried out at intervals of 1 to 2 days for the first 2 weeks after removal of the dressing. After this the intervals between observation were gradually increased to weekly observation for an additional month. Thereafter, the grafts were examined every 2 to 4 weeks or sometimes longer. Measurements of the graft were carried out from time to time. Skin was reciprocally transplanted between 4 pairs of the patients. In the 5 remaining patients, the skin was obtained from the abdominal incision of patients undergoing surgery for unrelated benign diseases.

RESULTS

The results of the skin tests for delayed bacterial sensitivity are shown in Tables I and II. In Table I the number of each of the skin tests performed and the number and per cent of positive reactions for each skin test are indicated. In Table II the results are expressed as a frequency distribution indicating the number of positive skin reactions at 24 and 48 hours in the Hodgkin's disease group and those patients not suffering from this disease. Expressed in either way it is apparent that the patients with Hodgkin's disease showed delayed allergic skin reactions much less frequently than did control patients. Indeed, whereas 64 per cent of the patients with Hodgkin's disease were completely anergic having no reactions to any of the antigens, only 1 per cent of the control group were nonreactors to the battery of antigens employed. There was 1 instance of notable immediate skin reaction which occurred in the control group. This did not affect the interpretation of the delayed reactions, however. The results of skin homografts in patients with Hodgkin's disease are summarized in Table III.

TABLE III.—SKIN HOMOGRAFTS IN PATIENTS WITH HODGKIN'S DISEASE

Patient	*Duration of graft*	*No. of positive skin reactions*	*Comment*
Adults			
1	13 months	0	Graft completely intact. No reactions
2	11 months	1	Graft partially intact. Protracted period of reaction, now stable
3	11 months	2	Partially intact, now stable. Previous protracted period of reaction
4	9 months	0	Partially intact. After initial take, reaction occurred in 2nd month lasting about 1 month. Now stable
5	9 months	2	Graft partially intact. Mild reaction beginning at 1 month. Now stable
6	7 months	0	Graft intact, but contracted. Died of his disease at 7 months.
7	4 months	0	Graft partially intact. Recent reaction, now stable
8	2½ months	0	Died at 2½ months; at that time graft partially intact, but still undergoing change
9	14 days	1	Sudden necrosis at about 2 weeks. Crust removed at 6 weeks with no evidence of surviving graft. Healing incomplete
10	18 days	4	Sudden necrosis at 18 days. Necrotic graft did not come off until 52 days. Healing now complete
Children			
1	3 months	0	Sudden slough between 9 and 12 weeks after transplantation
2	3 to 4 months	0	Slough of a gradual type beginning 3 months after transplantation
3	10 to 17 days	0	Rapid slough typical of homograft rejection in a normal person

Initially, all of the skin homografts took completely or nearly completely. Two of the grafts subsequently behaved as if they were autografts with only slight desquamation during early healing and later slight to moderate contraction with the passage of time. One of these grafts was observed until the death of the patient 7½ months after placement. The second graft remains intact 13 months following operation. In 8 instances the grafts have shown prolonged survival and abnormal rejection pattern. The latter was characterized by apparent early healing followed by subsequent late reaction which resulted in gradual loss of part or all of the homograft. This late reaction commonly appeared between 5 to 12 weeks after placement of the graft and manifested itself as the formation of red crusts which covered part or all of the graft, remained in place several

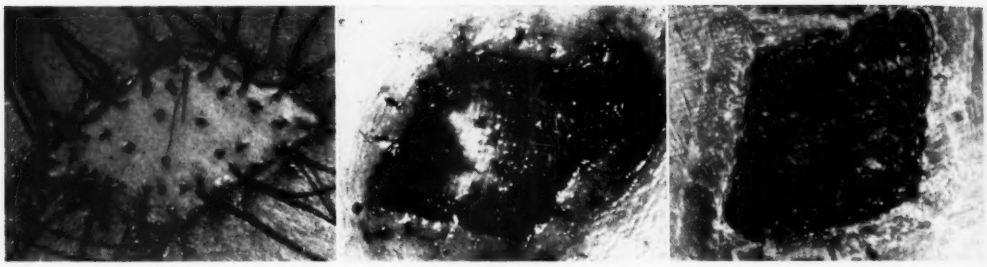

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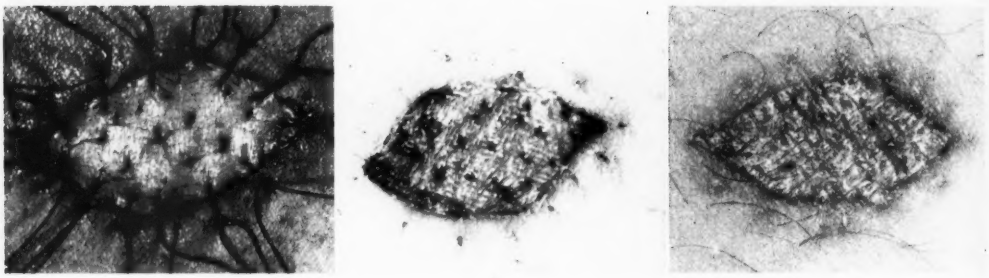
FIG. 1.



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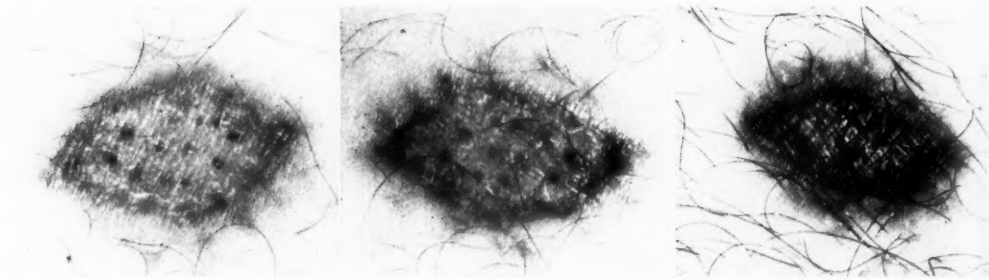

d e f

FIG. 2.

FIGS. 1 to 3. Representative examples of the 3 types of response to tattooed full thickness skin homografts, 1.5 by 2.0 centimeters, applied to patients with Hodgkin's disease.

FIG. 1. Early graft rejection: a, at operation; b, at 11 days, cyanosis and beginning necrosis; c, at 18 days, complete necrosis with desiccation and beginning slough.

FIG. 2. Behavior similar to autograft: a, at operation; b, at 2 weeks, excellent initial take; c, at 1 month, slight superficial desquamation; d, at 2 months, beginning slight contraction with broadening of peripheral scar; e, at 3 months, no change; f, at 7 months, further moderate contraction with widening of peripheral scar; this is the present appearance of the graft at 13 months following placement.

weeks, and then scaled off. In each of these reactions, there was little or no erythema of the surrounding host skin. When the crusts eventually came off, it was surprising to find the underlying area covered with intact epithelium with identifiable ink dots still present in the same pattern as that of their original placement. After several months of such reaction the remaining graft tissue appeared to survive without further sign of acute reaction. In 6 of these 8 patients, there have been persistent areas of tattooed skin

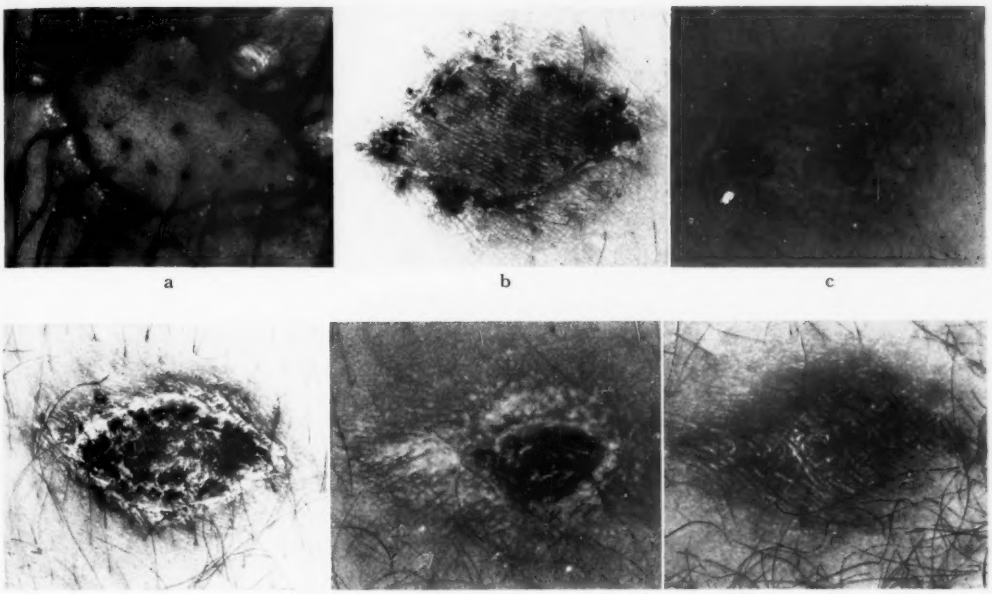

FIG. 3.

FIG. 3. Late reaction with partial loss of the graft: a, at operation; b, at 14 days, good initial take, slight necrosis of one tip; c, at 1 month, development of scale covering about half of the graft, necrotic tip still present; d, at 2 months, development of crusts about outer edges of the graft, moderate erythema of the surrounding host skin; e, at 3 months, peripheral portions of graft partially covered by scale, central portion of graft covered with a dark red crust; f, at 5 months, crust gone, but slight scale persists; 8 ink dots in the original pattern still visible; no further reaction in subsequent 6 months of follow-up study.

during the follow-up period (2½ to 11 months), whereas in 2 instances (both children) the late reaction resulted in apparent complete loss of the graft. In 3 cases (2 adults and 1 child) typical homograft rejection occurred between 2 and 3 weeks after grafting with sudden necrosis of the entire graft. Following slough, which was greatly delayed in the 2 adults (6 to 7 weeks) there was no evidence of persistent graft. In Figures 1 to 3 several forms of homograft reaction observed in this study are illustrated. Electrophoretic studies of serum proteins revealed that none of these patients was hypogammaglobulinemic. The formation of circulating antibodies in response to a battery of antigenic stimuli in each of the patients on whom studies of immunologic responses were carried out was normal.

COMMENT

The results of the skin tests confirm the observation of Schier and associates that patients with Hodgkin's disease possess a high incidence of anergy against delayed hypersensitivity to a battery of common bacterial and viral antigens. Our observations, to be reported elsewhere, indicate that in all 9 patients tested, including those who had one or more positive skin reactions in response to the battery of common antigens, new hypersensitivity of the delayed variety failed to develop with an adequate stimulus. This observation, if substantiated, helps to resolve the apparent inconsistency with theory, since in the small number of skin homografts performed no striking difference has been observed in the behavior of grafts placed on positive as contrasted with nega-

tive skin test reactors. The 2 skin grafts which behaved like autografts, however, were in patients having no evidence of delayed allergy whatsoever.

Skin homografts in normal unrelated humans usually survive less than 2 weeks. In closely related individuals and in persons with marked similarity of blood types, a somewhat longer period of homograft survival can be expected. Patients with extensive burns have been known to tolerate skin homografts for as long as 6 weeks prior to slough. Similarly, prolonged survival of skin homotransplants to uremic patients has been reported by Dammin and associates. In the cases reported herein, skin homografts have survived for periods well beyond those observed in any of these other situations. However, there is evidence that even in the patients with Hodgkin's disease many of the grafts are not completely acceptable to the recipients. Nevertheless, markedly prolonged survival of skin was regularly observed, and, in many instances, when rejection ultimately occurred an atypical rejection pattern was the rule in patients with Hodgkin's disease.

These observations seem best interpreted as providing indirect support for the view that delayed allergy plays an important role in the rejection of skin homotransplants in man. Obviously other interpretations might fit these observations and the ultimate analysis of these data must await more complete elucidation of the immunologic abnormality which is present in patients with Hodgkin's disease. Certainly, these data should not be interpreted as evidence indicating that the classical immune response involving antibody plays no role in homograft rejection.

It seems likely to us from these studies and from those previously presented from the laboratory describing prolonged survival of skin and lymph node homografts in agammaglobulinemic patients (2, 3, 8) that the homograft reaction may be a complex type of immunity in which both antibody and specific allergic cellular mechanisms play a role.

SUMMARY

1. Skin tests were carried out in 28 patients with Hodgkin's disease and 208 patients with various other diseases.

2. The following commonly encountered microbial antigens were used in performing the skin tests: (1) diphtheria toxoid, (2) streptokinase-streptodornase, (3) mumps virus, (4) mumps control solution, (5) Trichophyton gypseum, (6) Candida albicans, and (7) P.P.D., intermediate strength.

3. The results showed a high incidence of anergy (negative reactions) in the Hodgkin's group in contrast to the non-Hodgkin's group.

4. Skin homografts were performed in 13 patients with Hodgkin's disease.

5. In 2 patients observed for 7 and 13 months respectively, the homografts behaved essentially as autografts. In 8 patients the grafts survived the period during which homografts usually are rejected, but then exhibited late reactions beginning 1 to 3 months postoperatively which resulted in complete loss of 2 grafts and partial loss in six. In 3 cases typical homograft rejection occurred from 2 to 3 weeks postoperatively.

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REPORT OF SIX CASES OF CHONDROMYXOID FIBROMA OF BONE

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In 1948, Jaffe and Lichtenstein first described a rare bone lesion which they termed chondromyxoid fibroma of bone. This is a benign neoplasm apparently derived from cartilage-forming connective tissue and has distinct histologic characteristics. Jaffe and Lichtenstein expressed the opinion that some of these tumors have in the past been classified histologically as chondrosarcomas which was true in 2 of our patients. One of them had been regarded as a 15 year survivor of chondrosarcoma following amputation (Cases 1 and 2).

There have been 30 previously reported examples of chondromyxoid fibroma (Table I) and we are recording 6 additional cases (Table II).

This condition is most often seen in adolescents or young adults (Chart 1). Sex seems unimportant as there were 18 males and 18 females.

There is a definite predilection for bones of the lower extremity which was the site in all but 4 of the 36 cases. More than half of the cases involved the tibia or femur (Table III). Those of the fibula reported by us are the first in which this bone was involved.

The lesion, located in the metaphysis and often in adjacent portion of the diaphysis, usually gives rise to initial symptoms of pain and swelling though in some instances swelling was noted without associated pain. Symptoms evolve slowly and insidiously so that there is often delay of months or years from the first symptom before the first examination is made.

The appearance of this lesion on roentgenographic examination suggests that it is benign but it may be mistaken for central chondroma, benign chondroblastoma, bone cyst, or even fibrous dysplasia. The most important differential diagnosis is between chondromyxoid fibroma and chondrosarcoma.

The microscopic features of this disease may resemble a benign chondroblastoma. In 3 of Dahlin's cases there were coincident histologic features of both these lesions. Since the microscopic and gross pathology has been so well presented by Jaffe and Lichtenstein in their original communication it is not deemed necessary to discuss it further at this time.

Because this is a benign tumor composed of tissue that is not likely to be at all radiosensitive it follows that conservative surgery is indicated. Curettage with or without bone chip implantation is to be recommended in cases in which resection of the tumor-bearing portion of the bone is impractical. Resection is particularly applicable for fibula, ulna, rib, and metatarsal lesions. The method of treatment used in the 36 cases is shown in Table IV.

TABLE I.—PREVIOUSLY REPORTED CASES

Year	*Name of author*	*Cases*	*Bone involved*
1948	Jaffe and Lichtenstein	8	Femur 2, tibia 3, calcaneus 1, metatarsal 2
1948	Stradford	1	Tibia
1951	Goorwitch	1	Rib
1953	Dahlin, Wells, and Henderson (3)	2	Tibia, rib
1954	Hadders and Oterdoom	1	Tibia
1954	Wrenn and Smith	5	Femur 1, tibia 3, phalanx (toe) 1
1955	Benson and Bass	1	Thoracic vertebrae
1956	Dahlin (2)	11	Femur 2, tibia 4, pelvis 2, ulna 1, metatarsal 2
1948–1956	Total	30	

From the Bone Tumor Service, Memorial Cancer Center, New York.

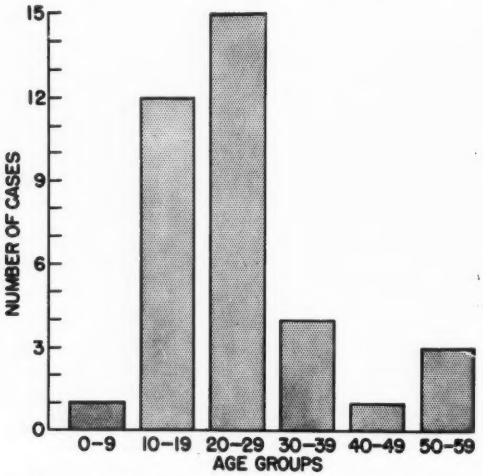

CHART 1. Age groups in 36 cases of chondromyxoid fibroma.

Based on follow-up studies in 32 of the 36 cases, ranging from several months to 18 years, it is found that 4 cases recurred and in 1 of these the specimen eventually revealed chondrosarcoma. This is the only reported case of chondrosarcoma secondary to chondromyxoid fibroma.

CASE REPORTS

CASE 1. M. K., a 31 year old white female, was admitted to the Bone Service of Memorial Hospital on November 11, 1941, with a chief complaint of pain in the right knee of 5 weeks' duration, which had steadily increased and which radiated down to the ankle. Upon examination the only abnormal finding was a slight swelling of the upper anterior aspect of the tibia which was quite tender. Roentgenograms were thought to indicate a giant cell tumor.

On November 19, 1941, the involved area was curetted and cauterized with zinc chloride. A sliding bone graft was then inserted. Immediate frozen section diagnosis was "myxochondrosarcoma, low grade."

Convalescence was uneventful and she was discharged on the seventeenth postoperative day in good condition. Since discharge the patient has been observed regularly in the clinic and was last seen in June 1957, more than 15 years after operation. She has full function of the extremity. In February 1956, the pathologic diagnosis was changed to "chondromyxoid fibroma."

This case, finally classified as chondromyxoid fibroma, is an example of the fact brought out by Jaffe in his original paper, namely that this lesion may be readily confused with chondrosarcoma.

CASE 2. S. J., 27 year old colored female, was admitted to the Bone Tumor Service of Memorial Hospital on April 11, 1943 with a chief complaint of swelling in the right ankle of 6 years' duration. On physical examination the only abnormal findings were swelling and tenderness of the right external malleolus. There was no lymphadenopathy. Prior to admission a biopsy had been made which had been reported as "low-grade chondrosarcoma."

On April 14, 1943 a resection of the distal end of the right fibula was performed and microscopic diag-

TABLE II.—MEMORIAL CENTER SERIES

Case Age Sex	*Bone involved*	*Sign and symptoms*	*Duration prior to operation*	*Treatment*	*Follow-up*
1. M.K. 31 F	Tibia, proximal R.	Pain and swelling	5 weeks	Curettage with cauterization	16 years
2. S.J. 27 F	Fibula, distal R.	Swelling	6 years	Resection of distal end of fibula	Pt. died due to tuberculosis
3. P.C. 12 M	Tibia, distal L.	Painless swelling	6 weeks	Curettage with bone chips	4 yrs.
4. Y.G. 51 F	Ilium R.	Pain	At least 1 month	Resection of involved segment of ilium	3 yrs. 9 mos.
5.*J.B. 17 M	Fibula, proximal L.	Pain	2 mos. 1 mo.	1. Resection 2. Amputation	1 yr. 7 mos.
6. C.R. 29 F	4th metatarsal shaft R.	Mild pain	2 mos.	Resection of 4th metatarsal of toe	Recent case

*This is the only case on record of chondrosarcomatous degeneration of a chondromyxoid fibroma of bone.

FIG. 1. Case 1. Chondromyxoid fibroma originally classified as chondroma. Recent review of sections places it definitely in chondromyxoid fibroma group.

FIG. 2. Case 1. Four years after curettage and sliding bone graft. Patient has normal function and no complaints 16 years later.

nosis was chondromyxoma. Convalescence was uneventful. The patient was discharged on the tenth postoperative day. Thereafter she was observed regularly in the clinic for 6 months and her condition was satisfactory. On May 1, 1944 the patient expired at Seaview Hospital where sputum examinations were reported as positive for tubercle bacillus.

On June 24, 1957, after reviewing the slides of the resected specimen, the original diagnosis was changed to chondromyxoid fibroma.

CASE 3. P. C., a 12 year old white male, was admitted to the Bone Tumor Service of Memorial Hospital on September 9, 1953. His chief complaint was painless swelling of the lower end of the left leg above the ankle, of 6 weeks' duration. On examination there was slight induration of the left ankle and tenderness on pressure. The entire ankle was enlarged. X-ray films revealed a multilocular cystic lesion of the distal end of the left tibia.

On September 10, 1953, the lesion was curetted and filled with bone chips. Pathologic diagnosis was "chondromyxoid fibroma." The patient was discharged in good condition on September 25, 1953, and since discharge his condition has remained very satisfactory and he has participated in baseball and wrestling.

The final diagnosis was chondromyxoid fibroma of the left tibia.

CASE 4. Y. G., a 51 year old white female, was admitted to the Bone Tumor Service of Memorial Hospital on February 10, 1954. Her only complaint was migrating pain between the right hip, knee, and ankle. One month prior to admission x-ray films were made which revealed a large osteolytic area in the right ilium. Skeletal survey and other examinations were negative. On examination there was a palpable firm fixed mass over the right iliac crest which had well demarcated borders and measured 10 by 4 centimeters.

Since aspiration biopsy had failed to determine the diagnosis an open biopsy was performed on February 15, 1954, and the diagnosis of chondromyxoid fibroma was established and confirmed. A resection of the involved segment of the ilium was performed on February 25, 1954, and the diagnosis on the resected specimen was chondromyxoid fibroma. The patient was discharged on the fifteenth postoperative day following an uneventful convalescence. Thereafter she remained symptom-free for 2½ years.

The final diagnosis was chondromyxoid fibroma of the right ilium.

TABLE III.—DISTRIBUTION OF 36 CASES OF CHONDROMYXOID FIBROMA

	Literature	*Memorial Center series*	*Total*	*Per cent*
Tibia	13	2	15	41.7
Femur	5	0	5	13.8
Metatarsal	4	1	5	13.8
Pelvis	2	1	3	8.3
Fibula	0	2	2	5.6
Rib	2	0	2	5.6
Phalanx (toe)	1	0	1	2.8
Ulna	1	0	1	2.8
Tarsal	1	0	1	2.8
Vertebrae	1	0	1	2.8
Total	30	6	36	100.0

TABLE IV.—TREATMENT OF 36 CASES

	Curettage	*Resection*	*X-ray therapy*	*Amputation*
Jaffe and Lichtenstein (1948)	8	0	0	0
Stradford (1948)	1	0	0	0
Goorwitch (1951)	0	1	0	0
Dahlin, Wells, and Henderson (3) (1953)	1	1	0	0
Hadders and Oterdoom (1954)	1	0	0	0
Wrenn and Smith (1954)	1	4	0	0
Benson and Bass (1955)	1	0	0	0
Dahlin (2) (1956)	10	0	1	0
Coley and Iwata (1957)	2	4	0	*1
Total	25	10	1	1

*This is the only case on record of chondrosarcomatous degeneration, and excision was done twice before amputation.

FIG. 3.

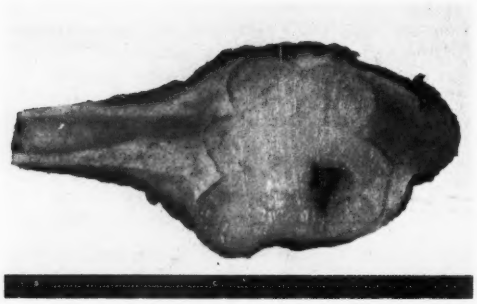

FIG. 4.

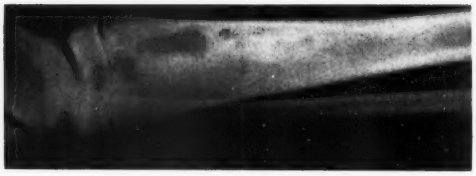

FIG. 5.

FIG. 3. Case 2. Chondromyxoid fibroma of fibula.

FIG. 4. Case 2. Gross specimen showing shiny, pale, glossy homogeneous appearance.

FIG. 5. Case 3. Chondromyxoid fibroma of tibia. Note extent of disease in metaphysis and distal diaphysis, and the loculated appearance.

FIG. 6.

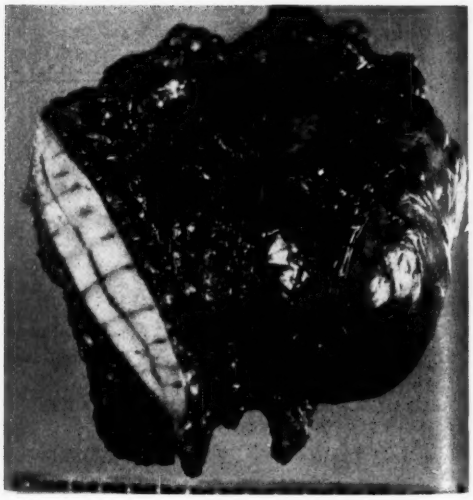

FIG. 7.

FIG. 6. Case 4. Roentgenogram shows chondromyxoid fibroma of ilium.

FIG. 7. Case 4. Photograph shows gross specimen of same case as illustrated in Figure 6. Note elliptical area of skin removed with specimen which was site of previous biopsy.

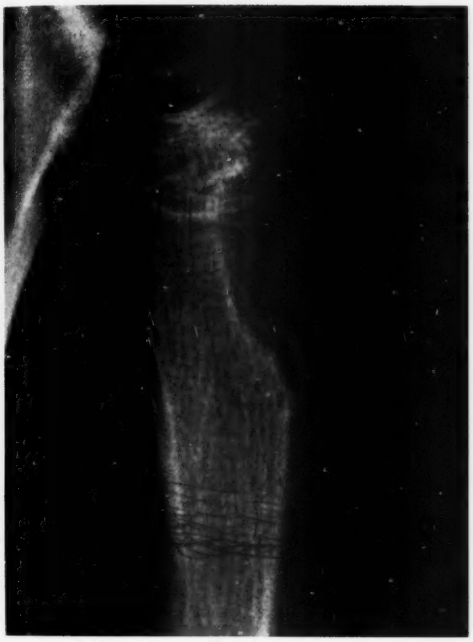

FIG. 8.

FIG. 8. Case 5. Chondromyxoid fibroma of proximal end of fibula. Note the similarity to aneurysmal bone cyst. This lesion underwent chondrosarcomatous changes and required amputation. Patient is free of disease 20 months later.

FIG. 9.

FIG. 9. Case 6. Chondromyxoid fibroma of metatarsal. Note the similarity of roentgenographic appearance to aneurysmal bone cyst. This patient was treated by excision.

CASE 5. J. B., a 17 year old white male, resident of Panama, was first admitted to the Bone Tumor Service of Memorial Hospital on October 2, 1955. His chief complaint had been pain of a severe, cramping nature referable to the right upper fibular region and lateral aspect of the leg. In November 1954 there had been a resection of a portion of the proximal fibula "because of a tumor," performed in a Panama hospital; thereafter he complained of pain, mild at first but becoming more severe during the preceding 2 months. At this time the tumor mass was noted to have recurred over the lateral aspect of the leg. On examination there was a well healed incision over the upper lateral aspect of the lower leg. Beneath the proximal portion of the scar there was a nodular irregular mass, 3 by 4 centimeters in size, fixed to the bone and immovable. There were no masses in the popliteal space. Sections from the tumor removed in Panama in November 1954 were reviewed by two pathologists; both made a diagnosis of chondromyxoid fibroma.

On October 3, 1955 an attempt was made to resect the entire tumor but because the operator hesitated to sacrifice the peroneal nerve the excision was incomplete and a portion of the growth which completely encircled the nerve was left behind. From this operation convalescence was smooth. The pathologic findings were chondromyxoid fibroma but some of this tissue was from outside bone.

Five months later (March 16, 1956) the patient was readmitted for a recurrence of the tumor, of 1 month's duration associated with mild pain. Two firm, irregular tumor masses were palpated beneath the scar of the previous operations. On March 21, 1956 the tumor mass together with the proximal fourth of the fibula was segmentally resected with deliberate sacrifice of the involved peroneal nerve. The specimen in the opinion of both Dr. Jaffe and Dr. Stewart revealed low grade chondrosarcoma. Following this report an amputation above the knee was performed on April 2, 1956. The specimen did not reveal evidence of residual disease. The patient made an excellent recovery and was discharged on the eighth postoperative day with a wound that had healed by primary union.

Examination in May 1957 or 13 months after am-

putation, failed to reveal any evidence of recurrence; a roentgenogram of the chest was negative for pulmonary metastases.

Final diagnosis was secondary chondrosarcoma arising on a chondromyxoid fibroma.

CASE 6. C. R., a 29 year old white female, was admitted to the Bone Tumor Service of Memorial Hospital on November 3, 1957, with a chief complaint of mild pain in the right foot of 2 months' duration. On examination the only abnormal finding was a slight swelling and mild pain in the area of the head of the right fourth metatarsal. X-ray film which was taken 2 weeks before admission revealed an irregular lytic lesion of the right fourth metatarsal bone. Prior to admission an aspiration biopsy had been made which was reported as "cartilaginous tumor, probably chondrosarcoma."

On November 4, 1957, a resection of the right fourth metatarsal and toe was performed, and microscopic diagnosis was "chondromyxoid fibroma." Convalescence was uneventful, and the wound healed by primary union.

SUMMARY

Six cases of chondromyxoid fibroma are reported including the case which revealed secondary chondrosarcomatous degeneration. The malignant transformation of this tumor has not been previously reported. The occurrence of this tumor in the fibula is also reported for the first time (2 cases). In order to avoid an unnecessary amputation one should bear in mind the possibility of mistaking chondromyxoid fibroma for chondrosarcoma.

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AN EXPERIMENTAL AND CLINICAL COMPARISON OF THE BUBBLE DISPERSION AND STATIONARY SCREEN PUMP OXYGENATORS

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THE CURRENT SURGICAL LITERATURE demonstrates well that a variety of mechanical principles can be employed to produce a satisfactory pump oxygenator for extracorporeal circulation. It is certain that in the brief period of 3 years open heart surgery during cardiac bypass has established for itself a permanent place in the field of surgery. Appreciation of this fact has led to a general interest in the performance of this type of surgery throughout the country. On the basis of currently available information, it is difficult for the surgeon to choose that method of extracorporeal circulation which will be safest for the patient and most economical and easy for him to use. For the majority of patients who have undergone cardiac bypass, either the bubble dispersion oxygenator described by De Wall and associates (2) or the stationary screen oxygenator of Gibbon has been used. The purpose of the present study is to compare these two types of oxygenators under experimental and clinical conditions.

Despite the practicality and economy of many of the devices for cardiac bypass, it is interesting to note that their clinical application is limited to relatively few medical centers. The reason is that many investigators have encountered an unexplained high mortality in experiments performed preparatory to the clinical use of cardiopulmonary bypass. Although attention to myriad details is essential to successful operation of a pump oxygenator, the present report will outline the major problems concerned with clinical use of cardiac bypass.

In a previous study from this laboratory (4), flow rates approaching a normal cardiac output were demonstrated to be superior to lower flow rates. The perfusion of peripheral tissues by relatively normal amounts of blood, and the maintenance of adequate perfusion pressures within the arterial system avoid the severe metabolic acidosis that occurs with the lower flow rates. For this reason, high flow rates were employed for all experimental and clinical perfusions reported herein.

METHODS

Sixty-five mongrel dogs, weighing between 7.2 and 15.5 kilograms, were employed in the experimental part of this study. Animals to be subjected to cardiac bypass were premedicated with morphine and atropine sulfate; anesthesia was induced with intravenous pentobarbital sodium. Dogs employed as blood donors were lightly anesthetized with ether to avoid addition of further barbiturate anesthesia to the extracorporeal circuit. Blood for priming the apparatus was collected in siliconized bottles containing 36 milligrams of heparin per liter. Postoperative transfusions were administered, when necessary, employing citrated dog blood.

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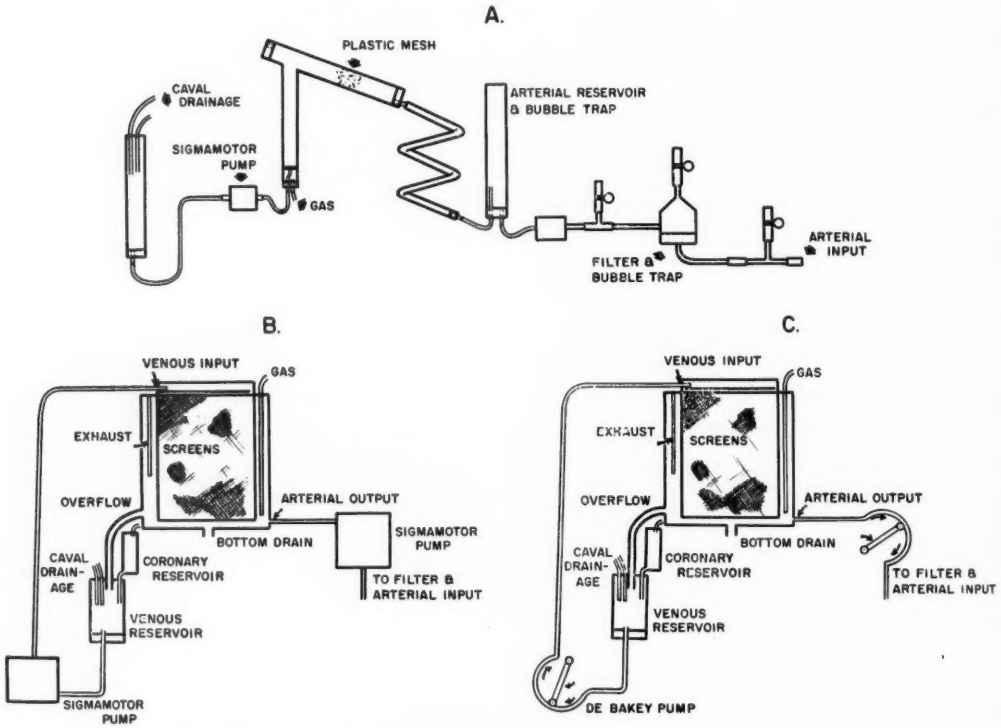

FIG. 1. Schematic drawing of extracorporeal circuits employed in this study. A, Dispersion oxygenator with Sigmamotor pump. B, Stationary screen oxygenator substituted for dispersion oxygenator. C, Stationary screen oxygenator with DeBakey pump.

Three types of pump oxygenators were used in these experiments: (1) The bubble dispersion oxygenator, described by De Wall and associates (2), was employed with slight modifications (Fig. 1A). Instead of the standard double blood filter, an 80 mesh, Monel metal screen was mounted in a plenum chamber to remove both particulate matter and air bubbles. A second air bubble trap was placed between the filter and the arterial cannula. In later experiments, a warming bath maintained at 37 degrees centigrade was used to surround the helical settling chamber. A special metal, electroformed, nickel-plated tube was employed as the arterial cannula, rather than the plastic tube described by these authors. (2) A stationary screen oxygenator of the Gibbon type was modified. This stationary screen oxygenator was substituted for the bubble oxygenator described (Fig. 1B). All other elements of the system remained the same as that described by De Wall and associates. (3) The stationary screen oxygenator mentioned was combined with commercially available roller pumps of the DeBakey type (Fig. 1C). The circuit of this pump is similar to model 3 of the Gibbon machine, rather than to that employed by Kirklin and associates. Unlike the original Gibbon apparatus, electronic regulation of blood volume in the extracorporeal circulation is not employed. Blood temperature is maintained at normal levels by infrared heating rather than by conduction heating as employed by Gibbon.

The superior and inferior venae cavae were cannulated separately, and drainage

was established by gravity flow into a venous reservoir located 30 centimeters below the animal or patient. The left subclavian or femoral artery was used for the arterial input.

Animals and patients were given 1.5 milligrams of heparin per kilogram of body weight intravenously just before initiation of extracorporeal circulation. At the conclusion of bypass, protamine sulfate was administered in doses of 2.0 milligrams per kilogram of body weight intravenously over a period of approximately 20 minutes. Additional doses of protamine were given, if delayed clotting time so indicated. In both animals and patients, careful postoperative observation was carried out, including continuous monitoring of arterial pressure and electrocardiogram for at least 6 hours following the termination of the operation. Usually, the heart was not opened in experimental animals, and recirculation of coronary sinus blood through the pulmonary circulation occurred during the time of bypass. In clinical use, coronary sinus blood was aspirated by a separate pump and returned to the extracorporeal circuit. The status of the patient's blood volume was checked by weighing the patient immediately before and after surgery. Blood volume regulation during bypass was found to be highly accurate, and adjustment of blood volume was rarely necessary as a result of this weighing technique.

RESULTS

Flow rates and biochemical changes. An experimental comparison of the effects of the bubble and screen oxygenators on serum chemistry was done during a 20 minute period of cardiac bypass. There was a mean decrease in serum *p*H of 0.1 unit with the bubble oxygenator. With the use of the stationary screen oxygenator, there was no statistically significant change in serum *p*H and lactate (a separate study of arterial pCO_2 demonstrated that a metabolic acidosis was not being concealed by a respiratory alkalosis, *vide infra*). Serum *p*H and lactate data are presented in Table I. As in a previous study of high flow rates with the bubble oxygenator, the screen oxygenator produced no change in serum glucose, potassium, or amino-acid nitrogen.

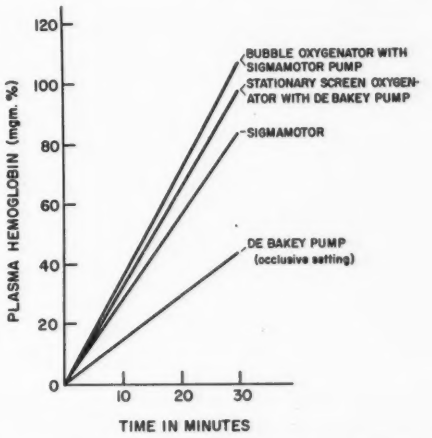

FIG. 2. Graphic demonstration of in vitro hemolysis.

Biochemical observations in patients confirmed the experimental studies.

Hemolysis. The most objective comparison of the red cell destruction produced by pumps and oxygenators can be obtained by in vitro experiments. Figure 2 presents a comparison of the Sigmamotor pump and bubble oxygenator with the DeBakey pump (set for total occlusion) and stationary screen oxygenator. The DeBakey pump clearly causes less hemolysis than does the Sigmamotor. However, the total hemolysis of the Sigmamotor pump combined with the bubble oxygenator is not significantly different from the hemolysis produced by the De Bakey pumps in combination with the stationary screen oxygenator. Although the screen oxygenator is less traumatic to the red blood cells than is the turbulence created in the bubble dispersion oxygenator by the mixture of blood and gas, the overall hemolysis figures for the two oxygenators are approximately the same. This is explained by the recirculation occurring in the Gibbon type apparatus, which pumps the blood several times over the stationary

TABLE I.—THE COMPARISON OF SERUM *p*H AND LACTATE BEFORE AND AT TERMINATION OF EXPERIMENTAL CARDIAC BYPASS WITH THE BUBBLE DISPERSION AND STATIONARY SCREEN OXYGENATORS

		pH				*Serum lactate, mgm. %*		
Type of oxygenator	*n*	*Before perfusion*	*At end of perfusion*	*p*	*n*	*Before perfusion*	*At end of perfusion*	
Bubble dispersion oxygenator	13	7.40±0.12	7.3±0.15	<.05	13	30.0±14.0	32.6±7.7	>.05
Stationary screen oxygenator	17	7.20±0.05	7.16±0.06	>.05	11	26.8±13.8	30.1±4.8	>.05

screens for each circulation through the patient. Serum hemoglobin levels in 8 patients perfused with the bubble oxygenator averaged 56 milligrams per cent; in 11 patients perfused with the screen oxygenator, the mean value of serum hemoglobin levels was 61 milligrams per cent.

Electroencephalogram. The electroencephalograph has proved a valuable and reliable safety device. On 4 occasions, obstruction of the venous or arterial cannulas, or other mechanical failures, prevented the delivery of adequate amounts of blood to the patient's arterial system. On each occasion, the first warning of technical difficulty came from the encephalograph.

An extensive preoperative and postoperative psychometric evaluation of these patients is being made by Fiske and Adams. These results will be reported upon elsewhere.

Oxygenation and carbon dioxide elimination. A theoretic approach to the problem of oxygenators indicates that the bubble device, because of the large area of blood-gas interphase, is a more efficient oxygenator. The diffusion area in the stationary screen oxygenator is limited by the number of screens employed. On the other hand, unlimited quantities of gas may be used with the screen oxygenator (unlike the bubble oxygenator) to establish the desired partial pressures of oxygen and carbon dioxide. Under practical conditions of operation, these theoretic considerations seem to be of little importance. Table II presents oxygen saturation data obtained in a series of animal experiments with the two types of oxygenators.

TABLE II.—OXYGEN SATURATION (IN PER CENT) EXPERIMENTAL COMPARISON OF BUBBLE DISPERSION AND STATIONARY SCREEN OXYGENATORS

Type of oxygenator	*n*	*Before bypass*	*At end of bypass*	*p*
Bubble dispersion oxygenator	4	101.8±7.7	85.4±12.5	>.05
Stationary screen oxygenator	4	104.1±3.3	97.4± 9.0	>.05

Although the saturation with the screen oxygenator was higher than with the bubble oxygenator, this fact seemed to have little practical significance. We have encountered no instance, either experimentally or clinically, in which an adequate level of arterial oxygenation could not be obtained with either type of machine. In order to compare the efficiency of the two types of apparatus in eliminating carbon dioxide from the blood, a mixture of 95 per cent oxygen and 5 per cent carbon dioxide was used in a small series of animal experiments with both types of machines. The use of 5 per cent carbon dioxide with the bubble oxygenator produced an increase in arterial pCO_2 of 6.3 millimeters of mercury in a 20 minute period of bypass. The use of 5 per cent carbon dioxide with the screen oxygenator caused a rise in pCO_2 of 19 millimeters of mercury. When the screen oxygenator is thus challenged by a diminished blood-gas pCO_2 gradient, it is less efficient in removing carbon dioxide than is the bubble oxygenator. From the practical point of view, this was of no significance, since the use of a 97 per cent oxygen-3 per cent carbon dioxide mixture in the screen oxygenator permitted maintenance of a normal arterial pCO_2 of 40 millimeters of mercury. It is concluded from these experiments that neither type of apparatus presents any problem with the introduction of oxygen into or the elimination of carbon dioxide from the blood.

Platelets. The comparison of the effect of the bubble and film oxygenators on the

platelet count was done in 6 animal experiments. With both oxygenators, there was a reduction in platelet count of 2.7 per cent per minute of bypass. The clinical data with the bubble oxygenator are inadequate for presentation. With the screen oxygenator, there was an average decrease of 1.1 per cent per minute. The lowest platelet count encountered in the clinical experience was 57,000 per cubic millimeter, a figure which is well above that of the hemorrhagic level.

EXPERIMENTAL SURVIVAL RATE

Previous studies showed a 41 per cent survival rate employing flow rates of 35 milliliters per kilogram of body weight per minute with the bubble oxygenator. These same studies showed no survival in a series of 14 animals perfused at 70 milliliters per kilogram of body weight per minute. The composite animal mortality from the literature with the bubble oxygenator (low flow rate) is 50 per cent. The survival rate of 41 per cent obtained in these experiments is lower than the 85 per cent survival rate reported recently by De Wall and associates (3). The lower survival rate reported here may be due to the fact that these experiments were performed approximately 3 years ago during our early experience with pump oxygenators. It may also be due to improper operation of the bubble oxygenator.

In order to delineate the exact cause of animal mortality with the bubble oxygenator, a stationary screen oxygenator was substituted for the bubble column and helix reservoir of the usual bubble oxygenator. This apparatus is illustrated in Figure 1B. The major value of this combination was to differentiate between experimental mortality due to tubing, cannulas, and "defibrination syndrome," and mortality due to the bubble dispersion oxygenator itself. With this device, the animal survival rate was 92 per cent in a series of 13 animals. It was quite apparent, therefore, that the previously noted mortality could not be attributed to the cannulas, tubing, anesthesia, or defibrination syndrome.

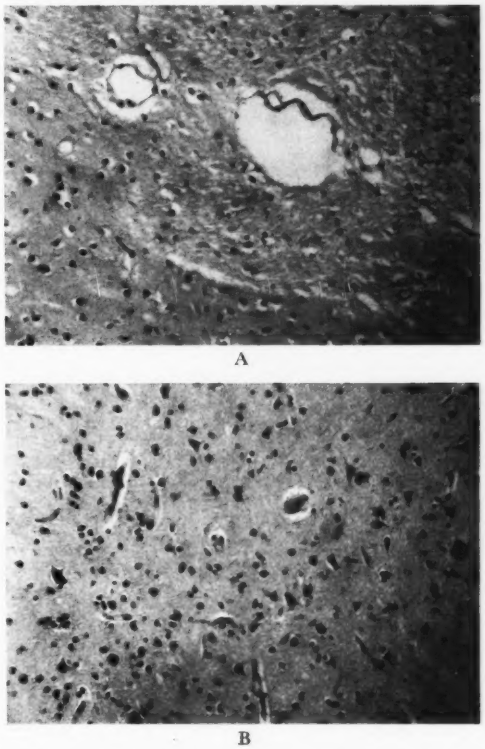

FIG. 3. Photomicrographs of human brain tissue after negative pressure fixation, ×63. A, Specimen from 4 week old infant perfused with the dispersion oxygenator. Note vacuoles due to air embolism. B, Control specimen from routine autopsy.

AIR EMBOLISM

The previously described experiments suggested that microscopic air embolism might be a factor in causing experimental mortality. Four types of experiments were designed, therefore, in an effort to detect air embolism occurring under experimental conditions.

1. A glass capillary tube with an internal diameter of approximately 300 microns was placed in parallel with the arterial input line during perfusion of the animal. By continuous observation of the capillary tube through a microscope, occasional masses of

FIG. 4. Schematic drawing of transseptal aspiration of air trapped in left ventricle after closure of ventricular septal defect.

globular foreign material were seen passing through the tube. It could not be determined whether this was air or antifoam material which had come from the defoaming chamber. In many experiments, despite prolonged observation, no such bubbles were seen.

2. A special method was designed to sample blood anaerobically from the aorta of dogs before, during, and after a 30 minute period of perfusion with the bubble oxygenator. Attached to each sampling chamber was a long capillary tube with an internal diameter of approximately 300 microns. Blood samples were placed immediately in a water bath at body temperature in the erect position, so that any gas collecting would be trapped and made easily visible in the capillary tube. Sixteen such blood samples were drawn from 4 different animals. All control samples, drawn either before or after perfusion, were negative for air bubbles. Specimens obtained during perfusion showed a single air bubble, approximately 500 microns in diameter. This volume of air had collected from approximately 1 milliliter of blood within the anaerobic chamber. The ease with which bubbles could be demonstrated varied with the ratio of the blood-gas mixture in the oxygenating column. These bubbles became larger with blood-gas ratios above 1:7 and became barely detectable at blood-gas ratios of 1:5. Control experiments with the stationary screen oxygenator were negative for air bubbles.

3. A plenum chamber of the type described in engineering textbooks was inserted in the arterial line. This plenum chamber served as an area in which, after a marked decrease in flow rate, microscopic air bubbles could collect at the top. By careful inspection of the transparent dome of the chamber, air bubbles, barely visible in size, were noted to collect whenever the bubble oxygenator was employed. The plenum chamber was the most sensitive method of detecting air embolism, since even at blood-gas ratios as low as 1:3, the minute air bubbles could always be demonstrated. In approximately 60 animal experiments and 80 clinical perfusions, such bubbles have never been noted with the stationary screen oxygenator.

4. Negative pressure tissue fixation technique. In a study of caisson disease, Schubert developed a method for the histologic demonstration of air emboli in tissues. This method was adopted for the purposes of the present study. In animals, biopsies of liver, kidney, and brain were taken before and after perfusion with both bubble and screen oxygenators. The tissues were placed in 15 per cent formalin in a chamber in which pressure was reduced to one-half atmosphere. Upon reduction of pressure, those specimens which had been perfused with the bubble oxygenator, especially the brain specimens, behaved as Cartesian divers; they floated to the surface where they remained as long as the negative pressure was maintained. The control specimens, taken before and after perfusion, and the specimens taken during perfusion with the screen oxygenator maintained a density greater than the formalin and, therefore, remained at the bottom of the chamber. After a 5 day period of fixation, routine histologic sections

were made. Ordinarily, air embolism is not visible on routine histologic sections. However, when subjected to one-half atmosphere pressure, microscopic air emboli will expand and cause disruption of the surrounding tissues. Fixation of these vacuoles will render them demonstrable on microscopic examination. All control specimens, taken before perfusion with the bubble oxygenator, and specimens taken from animals perfused with the screen oxygenator showed no evidence of air embolism. Of 10 animals subjected to perfusion with the bubble oxygenator, 5 showed definite evidence of air embolism; in 3, the evidence was equivocal; and in 2 negative. These data suggest that the extent of air embolism progressively increases as the blood-gas ratio is increased from 1:5 to 1:10. Air embolism could be demonstrated, whether or not a warming bath was employed around the helical settling chamber. Complete details of this experiment are presented elsewhere (14). Figure 3A shows evidence of air embolism in the brain of a 4 week old infant who died on the operating table after perfusion with the bubble oxygenator. A brain specimen, taken from a routine autopsy and subjected to the negative pressure tissue fixation technique, is illustrated for comparison (Fig. 3B).

PERFUSION SYNDROME

The major problem encountered by those who are beginning to work with experimental and clinical use of pump oxygenators is death due to what may be termed a "perfusion syndrome." As pointed out by DeWall and associates (3), this phenomenon is frequently accompanied by a hemorrhagic tendency characterized by continuous loss of blood from the pleural space into the chest drainage bottle.

Experimental syndrome. In the experiments with the bubble oxygenator, it was noted that the depth of anesthesia appeared to increase as soon as cardiac bypass started, despite the avoidance of barbiturates in the donor animals. With the screen oxygenator, the depth of anesthesia frequently diminished during bypass. The syndrome in animals is generally recognized within the first hour after completion of the surgical procedure. The animal awakens slowly, if at all. His general condition is characterized by areflexia and progressive hypotension. Death may occur within 1 to 24 hours. The hypotension fails to respond to administration of whole blood. This syndrome was fatal in 59 per cent of the animals in which the bubble oxygenator was employed at low flow rates. It is very interesting to note that with the use of the stationary screen oxygenator in more than 60 animals, there has never been a single instance of this perfusion syndrome.

Clinical syndrome. The clinical picture appears more related to central nervous system than to cardiovascular system pathology. It begins with a delayed reaction from anesthesia. Instead of awakening in the operating room within several minutes after discontinuance of anesthesia, the patient remains unconscious for periods up to 2 hours. There follows a semilucid interval of from 2 to 4 hours, during which the patient is in partial contact with the surroundings. Characteristically, there is a marked pallor of the facies. In contrast to the syndrome in animals, arterial blood pressure is ordinarily well maintained. The patients recover slowly over a period of 10 hours, or they may die suddenly from 4 to 8 hours after operation. It is usually difficult to know whether the patient's death is a result of failure of the respiratory or of the cardiovascular system. In 94 clinical cases, it was noted that all 14 patients who were operated upon with the bubble oxygenator showed the described syndrome in varying degrees. All patients showed a delayed reaction from anesthesia, pallor, and some restlessness. Ten of the 80 patients operated upon with the stationary screen oxygenator showed the syndrome. This difference in frequency is not necessarily attributable to the difference in the pump oxygenators, since all patients in our early clinical experience were

exceedingly poor risks, and all were operated upon with the employment of the bubble oxygenator.

A number of theories can be advanced to explain the perfusion syndrome. The experimental data presented suggest air embolism as a cause of this phenomenon. The fact that the syndrome has never been seen in the experimental animal when the stationary screen oxygenator was used gives strong support to the idea that microscopic air embolism produced by the bubble oxygenator causes neurologic damage. However, this conclusion is inconsistent with the clinical observation that the syndrome can occur with the employment of the stationary screen oxygenator.

Oxygen poisoning due to high partial pressures of the gas in the blood has been postulated to be a source of danger in the operation of pump oxygenators. Lambertsen's definitive studies support the consensus that oxygen toxicity does not occur at ambient pressures of one atmosphere (partial pressures of oxygen up to 713 millimeters of mercury. To eliminate oxygen poisoning as a possible explanation of the perfusion syndrome, we added nitrogen to the chamber of the screen oxygenator to maintain arterial pO_2 between 70 and 95 millimeters of mercury. Nevertheless, occasional instances of the perfusion syndrome were still seen in patients. Oxygen toxicity is, therefore, considered to be an unlikely explanation of the perfusion syndrome.

It has been suggested that a "defibrination syndrome" caused by rough surfaces within the pump oxygenator may produce fibrin depositions which undergo subsequent embolization. However, experimental comparison of the oxygenators, as illustrated in Figures 1A and 1B, would tend to eliminate defibrination as an explanation of the perfusion syndrome. Exchange of the stationary screen oxygenator for the bubble oxygenator certainly eliminated the syndrome in dogs, even though all cannulas, tubing, and other equipment remained the same.

The occurrence of metabolic acidosis during bypass has also been incriminated by Ito and associates. There is little doubt that a metabolic acidosis may occur during extracorporeal circulation, and that this acidosis is more severe with lower flow rates. However, the most severe acidosis reported in the literature with pump oxygenators is not nearly as severe as the respiratory and metabolic acidosis which has been reported by Beecher and Murphy as common in thoracic surgical cases. In the clinical cases of this series (perfusion rates between 70 and 110 milliliters per kilogram of body weight per minute), there has been no change in serum *p*H and lactate from pre-perfusion control levels. On the basis of these considerations, it is believed that the role of metabolic acidosis as an explanation of perfusion mortality has been overemphasized.

In analyzing our own experimental and clinical data with a view to explain the mechanism of the perfusion deaths, it is a striking fact that the perfusion syndrome, although sometimes observed in patients, did not occur in 60 animals perfused with the screen oxygenator. There were three differences between the experimental and clinical use of the stationary screen oxygenator: (1) in animal bypass, the heart was not opened and there was no opportunity for air to enter the left ventricle; (2) cardioplegia was not employed in animals, but was often used in the patients; and (3) in animals, cardiac action was allowed to return the coronary and bronchial blood to the general circulation, while in the clinical patients, this blood was returned by way of a special coronary aspirator.

To evaluate the role of these three factors in the production of the perfusion syndrome, a series of animal experiments was performed. The animals were placed on cardiopulmonary bypass and potassium citrate cardioplegia was induced. A ventricular septal defect was created and then repaired by interrupted suture. For the first time in our laboratory experience, 3 such animals developed a characteristic perfusion syndrome after bypass on the screen oxygenator. It was

found that this syndrome could be eliminated if, after closure of the ventricular septal defect and restoration of the heartbeat, the carotid arteries were clamped for a period of 45 seconds. Before restoration of the heartbeat, a needle inserted through the interventricular septum regularly demonstrated several milliliters of air in the most anterior portion of the apex of the left ventricle (Fig. 4). Such was the case, despite the fact that the final sutures closing the defect were tied under blood or saline. If cardioplegia was not employed, the beating heart tended to eject the air as the defect was closed. In our subsequent clinical experience, it has been possible to aspirate air from the left ventricle in almost every case in which cardioplegia was employed. The air was replaced with saline in each instance.

During clinical bypass, coronary blood was removed through a sump type aspirator (described by Donald and associates), placed in the right auricle, and returned to the venous reservoir. The use of a sump prevented occlusion of the aspirator tip by the atrial wall, but unfortunately, it also mixed the aspirated blood with air. Defoaming was accomplished in a special chamber containing shredded plastic coated with antifoam compound. Consideration of this coronary aspiration system, as suggested to us by Osborn, made it quite apparent that the foaming blood was the same factor which had caused the frequent occurrence of the perfusion syndrome in experimental animals. In subsequent clinical cases, therefore, the blood aspirated from the interior of the heart was returned to a large settling chamber and not reintroduced into the pump oxygenator until it had settled for a minimum of 10 minutes. The possible relationship of aspirated coronary blood to the perfusion syndrome was first demonstrated by the experimental work of Lillehei and associates (11).

CLINICAL RESULTS

The total clinical experience over a 2 year period with both types of oxygenator comprises 94 cases. Five patients with ventricular septal defect were operated upon with the bubble oxygenator. There were 3 operative deaths. The stationary screen oxygenator was used to close ventricular septal defects in 44 patients; there were 13 deaths. The remaining group was made up of patients with transposition of the great vessels, tetralogy of Fallot, atrioventricularis communis, total anomalous pulmonary venous drainage, and other complex defects. The mortality rate in this group of patients was 49 per cent.

Although the mortality rate in this series is high, it is apparent that most of the deaths occurred early in our experience. These cannot be attributed solely to the bubble oxygenator, which was employed exclusively in the first 14 patients of this series. Rather, the poor condition of the individual patient seems an equally plausible explanation. Most patients accepted for surgery had severe pulmonary hypertension, severe cardiomegaly, or intractable heart failure. Fifty per cent of the cases in this series fell into the 48 per cent mortality group (patients under 2 years of age, pulmonary artery pressure greater than 70 per cent of the aortic pressure) as defined by Lillehei and associates (12).

The elimination of air embolism and the selection of better risk patients have resulted in a current operative mortality rate of 30 per cent. This figure includes patients with complex cardiac defects, such as tetralogy of Fallot.

DISCUSSION

The experimental data presented in this article are interpreted to indicate that the screen oxygenator has some advantage over the bubble oxygenator in that it reduces the possibility of microscopic air embolism. Our clinical experience clearly demonstrates that factors other than the type of oxygenator employed may be of major importance. The excellent clinical results obtained with the bubble oxygenator (12) demonstrate that this device is capable of providing satisfactory extracorporeal circulation.

Our current preference for the screen oxygenator is, in part, due to the fact that a progressive increase in experimental mortality occurred with prolonged duration of bypass employing the bubble oxygenator. With the stationary screen oxygenator, we have detected no increase in mortality, either experimentally or clinically, with perfusion times up to 1 hour.

SUMMARY

An experimental and clinical comparison of the bubble dispersion and stationary screen oxygenators has been carried out. It is concluded that:

1. Metabolic acidosis does not occur in patients with the screen oxygenator at flow rates in excess of 70 milliliters per kilogram of body weight per minute.

2. Increase in plasma hemoglobin and decrease in the platelet count were approximately the same with the two types of oxygenator.

3. Experimental survival rate with the screen oxygenator is higher than with the bubble oxygenator, and this difference becomes more pronounced at higher flow rates.

4. By the following techniques, air embolism was demonstrated to occur with the use of the bubble oxygenator: (a) direct observation of a capillary tube placed in parallel with the arterial line, (b) an anaerobic sampling technique, (c) a plenum chamber, and (d) negative pressure tissue fixation technique.

5. A perfusion syndrome associated with cardiac bypass is described. It is characterized by areflexia, hypotension, confusion, and restlessness. This syndrome was demonstrated experimentally and clinically to be due to microscopic air embolism.

6. The occasional occurrence of the perfusion syndrome with the screen oxygenator was demonstrated to be due to air embolism originating either from a coronary aspirator system or from air trapped in the apex of the left ventricle.

7. The clinical use of cardioplegia was demonstrated to increase the likelihood of air embolism from the left side of the heart. Such embolism can be eliminated by the aspiration of air and replacement with saline following closure of ventricular septal defects.

8. Over-all clinical mortality rate from the use of both types of oxygenator in 94 patients was 52 per cent (41 per cent of the patients had ventricular septal defects; the remainder had transposition of the great vessels, tetralogy of Fallot, atrioventricularis communis, total anomalous pulmonary venous drainage, and other complex defects). Following the elimination of air embolism from the sources described in this experimental and clinical study, the operative mortality for the repair of complex intracardiac anomalies of all types has been 30 per cent (50 per cent of this latter group had ventricular septal defects; the remainder had more complex anomalies).

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CLINICAL EVALUATION OF A NEW ULTRASHORT-ACTING OXYGEN BARBITURATE FOR INTRAVENOUS ANESTHESIA

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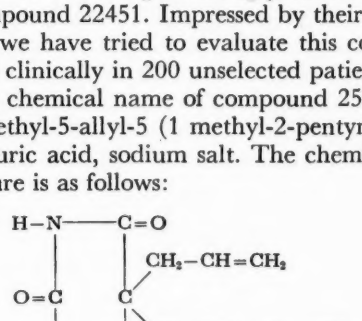
IN THIS AGE of fear and anxiety, the importance of reassuring a patient preoperatively cannot be overestimated. The promise of a smooth and pleasant induction of general anesthesia, the assurance that there will be no choking sensation before loss of consciousness and a quiet awakening with only pleasant memories are essential. To achieve this, intravenous thiobarbiturates are the drugs most often used. However, thiobarbiturates are parasympathomimetic agents, prone to cause laryngospasm, and, in some patients, bronchospasm. They may cause a significant fall in blood pressure even when most cautiously used. After prolonged use, there is a delayed awakening because thiobarbiturates are not a truly ultrashort-acting agent. Instead, they are rapidly deposited in the fatty depots of the body and subsequently slowly released as metabolism proceeds. This transformation is a slow process and consequently the thiobarbiturates only seem ultrashort-acting because of rapid localization in fats. This mechanism is temporary and eventually these substances are returned to the blood stream.

This is not true of the oxybarbiturates which are not predominantly localized in body fats but are almost completely metabolized, as shown for example for pentobarbital.

Cardiac responsiveness to vagal stimuli may be enhanced with the use of thiobarbiturates while most oxygen barbiturates show a parasympatholytic action. Frankel, in 1927, reported that, as a group, the thiobarbiturates are more toxic than their oxygen analogues. Therefore, it is not surprising that various oxybarbiturates, such as seconal sodium or nembutal sodium, have repeatedly been recommended and used for intravenous anesthesia, and they certainly have their place in our armamentarium. They are especially valuable for use with asthmatic patients in order to avoid bronchospasm or to reduce the amount of thiobarbiturate necessary when noninflammable drugs must be used for a long time. However, while seconal and nembutal are "short-acting," thus far there has been no "ultrashort-acting" oxybarbiturate available.

In their search to develop an ultrashort-acting oxygen barbiturate, Chen and his associates have tested over 2,000 barbiturates. The product of this search is compound 25398 the high melting point isomer of compound 22451. Impressed by their reports, we have tried to evaluate this compound clinically in 200 unselected patients.

The chemical name of compound 25398 is 1-methyl-5-allyl-5 (1 methyl-2-pentynyl) barbituric acid, sodium salt. The chemical structure is as follows:



COMPOUND 25398

1-methyl-5-allyl-5 (1-methyl-2-pentynyl) barbituric acid

From the Department of Anesthesiology, Mt. Sinai Hospital, and the Department of Surgery, Chicago Medical School, Chicago.

Compound 25398 is a white crystalline solid which is rapidly and easily soluble in water. It is stable in aqueous solution at 5 degrees for 1 year and at 25 degrees for 6 months. The *p*H ranges between 10 and 11.

LABORATORY RESEARCH

Preliminary studies at the Lilly Laboratories using cats, mice, rabbits, monkeys, and dogs, showed compound 25398 to be 3 times as potent, one-half as long in action, and much less likely to show accumulation, than thiopentobarbital. The compound did not produce venous irritation or hemolysis of the blood at any time during these investigative studies. The duration of action, the median anesthetic dose (AD_{50}), and the median lethal dose (LD_{50}) of compound 25398 have been determined by intravenous administration in rats (Table I).

PREVIOUS CLINICAL RESEARCH

The compound was previously used by Stoelting in 285 unselected patients. In human beings, it proved to be 3 times as potent as pentothal sodium and 4½ times as potent as surital sodium. The compound was utilized approximately 3 times as rapidly as pentothal sodium, and serious complications were not encountered.

A comparison of thiopental sodium, methitural sodium, and compound 25398 was also made by Redish and associates in patients undergoing oral surgery. In this study, the side effects of 25398 were reported to be about equal to those encountered with thiobarbiturate, but less than those seen with methitural sodium. Electroencephalographic tracings were similar to those produced by sodium pentothal. No preconvulsive electroencephalographic patterns were seen in either cats or humans by using 25398, the high melting point isomer, in contrast to some such electroencephalographic patterns produced with the use of oxybarbiturate 22451, the original material. The short duration of action and lack of accumulation demonstrated for 22451 proved the same for the high melting point isomer

TABLE I.—MEDIAN DOSES OF COMPOUND 25398

Compound 25398	*Median doses, mgm./kgm. of rats*
Anesthetic dose ± SE	12.1 ± 0.8
Lethal dose ± SE	22.8 ± 1.1

Average duration of action 31 minutes.
SE, standard error.

25398. Jactitations were seen on 3 occasions (2 patients) with 25398. No similar effects were noted with the other drugs. Electroencephalographic studies of these 2 patients demonstrated a deviation from normal in the brain wave pattern. This observation suggested to the authors that administration of 25398 might provoke seizures in patients with incipient epilepsy.

PRESENT STUDY

In the present study, compound 25398 (methohexital sodium) was administered to 200 unselected patients. All the patients were sedated preoperatively according to age and general condition. The usual combination of demerol hydrobromide, or morphine sulfate with atropine sulfate, or scopolamine hydrobromide, was given 1 to 1½ hours prior to the operation. In addition, doses of phenergan varying from 12½ to 25 milligrams were used in one-third of the patients 1 and 1½ hours prior to surgery.

TECHNIQUE OF ADMINISTRATION

For the intermittent intravenous injection technique, a 1 per cent solution of the compound was used. For administration by continuous intravenous drip, a 0.2 per cent solution was prepared.

If the compound was used for induction only, injection was stopped when the lid reflex was obtunded and inhalation of cyclopropane, ether, or both then was begun. If the compound was the sole agent or was used with nitrous oxide analgesia, injection of the 1 per cent solution was continued intermittently or, even more satisfactorily, the drip method was used throughout.

Relaxation, if needed, was supplied by relaxing agents, either succinylcholine by drip or one of the longer acting agents by intravenous injection. Seventy-seven patients in

TABLE II.—DRUGS USED

Agents	*No. of patients*
Cyclopropane	50
Ether + cyclopropane	67
Nitrous oxide	66
Oxygen	12
Ether	1
Others	4

TABLE III.—AMOUNT OF DRUG USED

Amount drugs, mgm.	*Induction, 1% solution No. of patients*	*Drip, 0.2% solution No. of patients*
0– 50	20	2
51–100	112	6
101–200	9	18
201–300	...	11
301 or more	...	38

this series were intubated orally, and in all of them, succinylcholine was used according to plan. Table II shows the inhaling agents used together with the compound and the number of patients in whom they were used.

Table III shows the amounts of the compound in milligrams used for induction and for maintenance respectively.

The types of operation, the ages and sexes of the patients, and duration of the procedures in hours are shown in Table IV.

One hundred and twenty-eight of the patients were rated in good condition (64 per cent), 53 as fair (26.5 per cent), and 19 patients were in poor condition (9.5 per cent) preoperatively.

CLINICAL RESULTS

Smooth rapid induction was achieved in all cases, accompanied by relaxation of the mandible, so that a pharyngeal airway could be easily introduced. In 22 patients, less than 50 milligrams of the compound were used; more than one-half of the patients needed between 50 and 100 milligrams for induction of anesthesia; while in 9 patients between 100 and 200 milligrams were used. For maintenance of anesthesia in prolonged cases, total doses up to 1,000 milligrams were needed and well tolerated by using the drip method. The average amount in these cases was 400 milligrams. The highest amount (1,000 mgm.) was used in 3 operations: a thoracotomy lasting 2 hours 10 minutes; a laminectomy (3 hours 10 minutes); and a bilateral herniorrhaphy (2 hours and 45 minutes). No ill effects were noted in these patients; they awoke promptly after termination of anesthesia.

There was no laryngospasm or bronchospasm noted during induction although the drug was administered to known asthmatic patients.

Hiccough was present in 4 patients, but deepening of the anesthesia (2 patients) or use of a relaxant (2 patients) overcame the difficulty.

Excitement after loss of consciousness with slight convulsive type movements was noted in 2 patients and watched very carefully on account of previous clinical research. However, deepening the anesthesia by adding more of the compound put both patients into quiet clinical anesthesia. There was no postoperative excitement present in these patients.

There was no local irritation or thrombosis noted at the site of injection in any patient, even in the case in which massive infiltration occurred in one arm during a spinal fusion. A short period of apnea occurred occasionally after rapid injection of the compound; and depressed breathing had to be corrected in 8 patients by positive pressure respiration with oxygen.

According to our routine handling of patients under general anesthesia, assisted respiration was used during maintenance in every patient except those in whom the drug was used to provide analgesia only. A drop in systolic blood pressure of 10 to 20 millimeters of mercury occurred in 22 patients after induction. This was of short duration and, as soon as oxygen inhalation was started or intubation was accomplished, the blood pressure reading returned spontaneously to the previous level.

There was 1 death in this series, postoperatively, but totally unrelated to the use of the new compound.

Special cases. The compound proved very satisfactory in inducing and maintaining analgesia by the slow drip method; it was thus used in cardiac catheterization; for

TABLE IV.—TYPES OF OPERATION

Type of operation	No. of cases	Ages, yrs.				Sexes		Duration of operation, Hours			
		0–16	17–30	31–50	51–	F	M	0–½	½–1	1–3	3–
Gynecologic	34	1	12	19	2			11	11	11	1
Thoracic-heart	7	1	1	4	1	3	4	0	0	6	1
Neurosurg.	17	1	1	7	8	9	8	8	1	5	3
Gen. surg.	70	5	10	27	28	39	31	13	12	46	9
G.U.	15	0	1	4	10	5	10	8	1	6	0
E.E.N.T.	9	4	1	3	1	5	4	1	2	5	1
Orthopedic	10	0	1	3	6	7	3	5	3	2	0
Dental	1	0	0	0	1	1	0	0	0	1	0
Others	37	4	11	15	7	22	15	11	17	9	0
	200										

bronchoscopy (utilizing topical anesthesia beforehand and enough d-tubocurare to minimize the strength of the handgrip of the patient); and for supplementing unsatisfactory spinal analgesia. In these cases, the patients were conscious, obeyed commands, but were quiet and had complete retrograde amnesia postoperatively.

COMPLICATIONS

A 28 year old patient scheduled for mitral commissurotomy had been premedicated with 25 milligrams of phenergan hydrochloride, 50 milligrams of demerol hydrochloride, and 0.5 milligram of atropine sulfate 1 hour preoperatively. Eight cubic centimeters of 1 per cent solution of the compound were used for induction of anesthesia. After thorough oxygenation the patient was intubated by using 40 milligrams of succinylcholine, and ether inhalation was started. Blood pressure was adequate until the patient was placed on her right side in a modified jackknife position. Systolic blood pressure then dropped from 90 millimeters of mercury, first to 70 and then to 60 millimeters. Levophed had to be administered during the rest of the operation in order to maintain the blood pressure. At the end of the operation, the patient was awake and turned on her back; blood pressure remained stable at the preoperative level without levophed. This patient had received cortisone preoperatively and received it during the operation. Recovery was uneventful.

A second patient, scheduled for mitral commissurotomy, 42 years old, diabetic, who was inducted and maintained with the compound (a total of 380 c.c. of a 0.2 per cent solution by drip) did well during surgery in spite of a transient drop in blood pressure and pulse irregularities when the mitral valve was explored, as evidenced in the electrocardiogram. At the end of the operation, the patient reacted to the endotracheal tube and was extubated. He developed pulmonary edema in the recovery room which responded promptly to oxygen-alcohol inhalation after reintubation and suction. There was delayed return of consciousness but the patient responded to stimuli. He was fully awake 2 hours later. Further recovery was uneventful. In this type of cardiac surgery, it is hard to evaluate the role, if any, which the compound might have played in contributing to the pulmonary edema. There was no obstruction of the airway during surgery; the lungs were being inflated adequately, respiration was active throughout, and seemingly well assisted.

The next patient was a 62 year old, very obese female, weighing over 200 pounds who came to the operating room for emergency surgery for an uncontrollably bleeding gastric ulcer. She suffered from a chronic organic cardiovascular disease; the electrocardiogram showed auricular fibrillation and auriculoventricular block. Hemoglobin, in spite of numerous transfusions, was 9.3 grams per 100 cubic centimeters. Her blood pressure was 90/60 upon arrival in the operating room. After induction with 100 milligrams of the compound followed by 40 milligrams, anectine endotracheal intubation was easily accomplished with a cuffed tube and further anesthesia, and relaxation

was supplied by slow anectine drip and minimal doses of ether in the circle rebreathing system. Respiration was active and was assisted throughout. A blood transfusion had been started at the beginning of the operation; however, the blood pressure had dropped to 70/50 shortly after induction and intubation and had to be maintained on the preoperative level with levophed. Though the patient was a known asthmatic, no wheezing or bronchospasm occurred during surgery. Patient was awake ½ hour after surgery and apparently out of shock.

A 57 year old man, suffering from multiple sclerosis and hypertension, presented prolonged unconsciousness. He had been given 25 milligrams of phenergan, 50 milligrams of demerol, and 0.5 milligram of atropine preoperatively. The operation was transurethral resection and lasted 1 hour and 10 minutes. Nitrous oxide analgesia and a total of 600 milligrams of the compound was given during an uneventful induction and maintenance of anesthesia. Condition after surgery was good, reaction to stimuli present, but the patient was not fully awake until 1½ hours after surgery.

SUMMARY AND CONCLUSION

A new ultrashort-acting oxybarbiturate methohexital sodium (25398) seems to come up to expectations. In this series of 200 unselected cases, it provided smooth rapid induction, adequate maintenance, and prompt awakening with the use of either a 1 per cent solution for intermittent intravenous injection or a 0.2 per cent intravenous drip. Amounts of the drug necessary for the purpose are small as compared with the thiobarbiturates. The drug seems to be metabolized quickly. It supplies good jaw relaxation, so that a pharyngeal airway can be introduced early. Laryngospasm did not occur in this series. The compound provides an adequate state of analgesia; this is best achieved by the slow drip method. The compound can be used in connection with the usual inhalants and relaxants. No convulsions occurred in this series, and no venous irritation at the site of the injection was noted.

Compound 25398 seems to be a safe agent in the hands of the experienced anesthetist. It deserves further evaluation.

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THE RELATION OF ENERGY, VELOCITY, AND ACCELERATION TO SKULL DEFORMATION AND FRACTURE

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RELATIVELY FEW STUDIES have been made of the forces responsible for head injuries, especially fractures, although a recent survey by Braunstein and associates revealed that in 1,678 individuals hurt in automobile accidents the head received some degree of injury in 75 per cent of the cases. Engineers have attempted to study the mechanism of skull fracture and the force involved in its production by the use of anthropomorphic dummies and by bouncing plastic head forms off of steel plates. The information obtained from the use of anthropomorphic dummies has some value because the dummies can be standardized. However, there is no such thing as a standardized human and a plastic head form is a far cry from an actual human head. Furthermore, the materials of which the dummies and head forms are constructed are much more homogenous than a human body which consists of such different materials as bone, muscle, fat, soft organs (e.g., heart, lungs, stomach), nerves, blood, tissue fluid, and water, each with its own physical properties and biomechanical behavior under loading. The human body is far too complicated to duplicate in any model or dummy, and there is no substitute for testing actual human material if one wishes to study its physical properties or biomechanical behavior under various conditions. The latter is especially important for safety engineering and Kulowski has emphasized that "crash-impact engineering and design may be stated to be an equation between human tolerance and decelerative forces (mechanical variables). From that standpoint the first line of defense becomes the limits of factors of safety of the human body."

Most head injuries, especially in automobile accidents, arise from blows or impacts which involve problems of energy, velocity, and deceleration or negative acceleration as the engineers prefer to call it. As pointed out by Lissner and Evans, head injury results from the absorption of energy which occurs whenever the head comes in contact with an object moving at a different velocity. Such an event may occur under three possible conditions: (1) the resting head, although free to move, may be struck by a moving object and be accelerated, (2) the moving head may strike a resting object and be decelerated, (3) the moving head strikes or is struck by a moving object. In this instance the head may be accelerated or decelerated depending on whether the head or the object is moving the faster and also on the relative masses and directions of each. The injury to the head will be identical in each of the three conditions if the location of the blow on the head and also the relative velocity between the head and the object is the same.

The present investigation was undertaken to determine, under controlled experimental conditions, the relation of energy, velocity, and deceleration to skull fracture.[1] However, as emphasized by Lissner and Evans (loc. cit), it should be remembered that "there is no correlation between the sever-

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TABLE I.—FREE FALL TESTS OF HUMAN CADAVER HEADS

Test	Cadaver data	Head wt., lbs.	Distance dropped, ft.	Values computed from theory: Velocity, ft./sec.	MPH	Energy, ft. lbs.	Remarks
1	59 W M	8.25	16.25	32.5	22	134	Fracture, probably from fall on concrete floor. No test
2	N M	7.38	20.17	36.2	24	148.7	No fracture
3	W F	6.88	20.17	36.2	24	138.6	No fracture
4	Same as test 2	7.38	30.75	44.6	30	226.8	No test. Head hit projection
5	Same as test 2	7.38	30.75	44.6	30	226.8	No fracture
6	Same as test 2	7.38	30.75	44.6	30	226.8	No fracture
7	W M	7.50	42.42	52.4	36	318.1	Fracture
8	57 W M	8.25	42.25	52.3	36	348.6	Fracture
9	Same as test 2	7.38	42.67	52.5	36	314.7	No fracture
10	60 W M	10.0	42.67	52.5	36	426.7	No fracture
11	68 W M	8.0	42.67	52.5	36	341.4	No fracture

The computed theoretic velocities and energies are reasonably correct.
F = female; M = male; W = white; N = Negro; MPH = miles per hour.

ity of cerebral damage and the production of linear skull fracture." Thus, skull fracture may occur without brain damage or concussion, and death may result without skull fracture. Consequently, merely preventing skull fracture does not insure complete safety or protection of the brain.

MATERIALS AND METHODS

The material used in the study consisted of intact human heads taken from adult embalmed cadavers. Each head before testing was weighed and roentgenograms taken of it to determine if any fractures or defects of the skull were present.

The tests consisted of dropping the heads through various measured distances upon a 1954 Ford instrument panel mounted in a way similar to that in the intact automobile. Each head was dropped so that the blow was applied to the forehead such as frequently occurs in automobile accidents when the head strikes the instrument panel. After each test roentgenograms were taken of the head again to determine the extent of the damage produced by the test. The tests thus fulfilled the requirements of the second condition mentioned previously. High speed motion pictures (1,000 frames/second) were taken of each head at the instant of impact.

A total of 28 tests, divided into two types, free fall and guided fall, were made. In the free fall tests the head was simply suspended at various distances over the panel upon which it was dropped by cutting the supporting cord. In the 10 free fall tests, the velocity, in feet per second and miles per hour, was computed from theory.

In the guided fall tests, the head was suspended from a steel triangular frame sliding on three guide wires. Each head had a circular area of the scalp removed from the occiput so that a Statham 500 g capacity accelerometer could be screwed directly onto the occipital bone. The accelerometer was in turn connected to one channel of a two channel oscilloscope and from the record thus obtained the magnitude of the acceleration and its duration were determined. In the first 11 tests of this type the frame had a tendency to bind so that the actual values of velocity and energy were lower than the theoretic values. Therefore, 6 additional tests were made with a modified frame which did not bind appreciably. In these tests an electronic switch was fastened to one of the guide wires at a point 2.5 feet above the point of impact on the panel. The switch, which was opened by the passing frame, was connected to the second channel of the oscilloscope and from the

record obtained the actual velocity of the head could be accurately determined.

In all the tests it should be emphasized that most of the available kinetic energy of a test was expended in denting the instrument panel, only a relatively small amount being used to produce skull deformation or fracture. In this respect the present tests are quite different from the earlier studies of Gurdjian, Webster, and Lissner (3) in which various types of linear skull fractures were experimentally produced by dropping intact cadaver heads upon a 160 pound steel slab 3 inches thick. In these studies, to all intents and purposes, all the available energy of a test was expended in deforming the head because the amount of energy, if any, absorbed by the steel slab was negligible.

RESULTS OF THE TESTS

Free fall tests. Eleven free fall tests were made with the heads of 5 white males, 1 Negro male, and 1 white female. The heads varied in weight from 6.8 to 10 pounds and were dropped through distances of 16.25 to 42.67 feet. The total available kinetic energy varied from 134 to 426.7 foot pounds, and the velocity from 32.5 to 52.5 feet per second (22 to 36 miles/hour). The head of the Negro male was tested 5 times without fracture but fractures were produced in the initial drop in the following tests: 1, 7, and 8 (Table I).

The first fracture (test 1), produced in the head of a white male 59 years of age, was considered as "no test" in the final consideration of the results of the experiments because the head bounced off the instrument panel onto the concrete floor.

A second fracture (test 7, Table I) was produced in the frontal and temporal bones of a white male of unknown age. The fracture (Fig. 2) originated in the middle part of the frontal bone and extended obliquely posteriorly and inferiorly, on the right side, to the anterior part of the temporal bone. The head had a velocity of 52.4 feet per second (36 miles/hour) and a total kinetic energy of 318.1 foot pounds at the instant of impact.

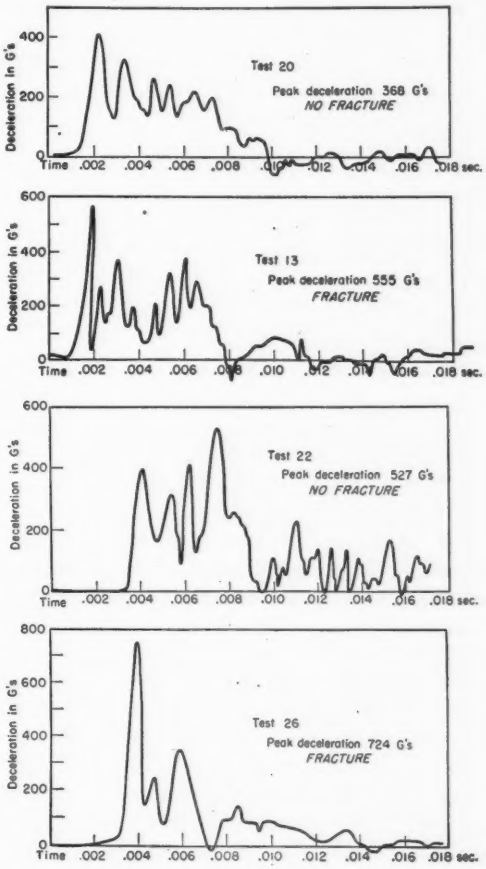


FIG. 1. Oscillograph records of skull deformation at impact.

The third fracture (test 8, Table I) occurred in the head of a white male 57 years of age at a velocity of 52.3 feet per second (36 miles/hour). The total kinetic energy available at the instant of impact was 348.6 foot pounds. The fracture (Fig. 3) was an extensive stellate type involving the frontal and parietal areas and extending bilaterally into the floor of the anterior and middle cranial fossae. Anteriorly in the frontal area there was also found a large depressed fragment.

TABLE II.—GUIDED FALL TESTS OF HUMAN CADAVER HEADS WITH THE ORIGINAL FRAME

Test	Cadaver data	Head wt., lbs.	Distance dropped, ft.	Computed values: Velocity, ft./sec.	Computed values: MPH	Computed values: Energy, ft. lbs.	Measured values-film: Velocity, ft./sec.	Measured values-film: MPH	Measured values-film: Energy, ft. lbs.	Peak acceleration, g ft./sec.²	Total time duration of acceleration, sec.	Remarks
12	N M	8.63	55.88	60.0	41	481.9						Fracture
13	N M	7.50	55.88	60.0	41	419.1	48	32.7	268	555	0.00903	Fracture
14	W F	6.88	55.88	60.0	41	384.1				321	0.0096	No fracture
15	60 W M	7.56	55.88	60.0	41	422.0				180	0.0092	No fracture
16	W M	9.25	55.88	60.0	41	516.8				196	0.0075	No fracture
17	64 W M	9.38	67.88	66.3	45	636.0						No fracture
18	W M	9.50	67.88				43.5	29.6	279	232	0.0117	No fracture
19	60 W M	8.13	67.88	66.3	45	552.0	59.2	40.3	443	346	0.00885	No fracture
20	W F	6.63	79.92	72.0	49	530.0	57.3	39.0	338	368	0.00885	No fracture
21	64 W M	8.75	79.92	72.0	49	700.0	58.9	40.1	473			No fracture
22	W M	8.50	79.92	72.0	49	680.0	57.3	39.0	434	527	0.00625	No fracture

F = female; M = male; N = Negro; W = white.

Guided fall tests with the original frame. The 11 heads used in this series of tests (Table II) varied from 6.63 to 9.50 pounds in weight and were dropped through distances of 55.88 feet (5 tests), 67.88 feet (3 tests), and 79.92 feet (3 tests). The velocity of the head at impact, measured from the high speed motion picture film, varied from 43.5 to 59.2 feet per second (29 to 40 miles/hour) in the 6 tests in which it was determined. The available kinetic energy at the instant of impact ranged from 268 to 473 foot pounds in the same tests. The peak acceleration had a range of variation from 180 to 555 g (g = 32.2 ft./sec.²) and the total time duration of the acceleration varied from 0.00625 to 0.0117 second in the 8 tests for which these data were obtained.

The only fractures produced in this series of tests occurred in the heads of 2 Negro males, of unknown age. In the first head (test 12, Table II) 2 linear fractures occurred in the central part of the left occipital bone and extended from there into the parietal bone and the lateral margin of the foramen magnum (Fig. 4). The head had a velocity of 60.0 feet per second (41 miles/hour) and an available kinetic energy of 481.9 foot pounds at the instant of the impact.

In the second head (test 13,) the frontal bone had an extensive comminuted fracture which extended to the right and left of the midline (Fig. 5). At the instant of impact the head had a velocity of 48.0 feet per second (32 miles/hour) and a kinetic energy of 268 foot pounds. A peak acceleration of 555 g with a total time duration of 0.00903 second was recorded.

The frame used in this series of tests sometimes had a tendency to bind. Consequently, the values for velocity and energy computed from a theoretic free fall (Table II) are generally too high.

Guided fall tests with a modified frame. Six additional tests (Table III) were conducted with the frame modified so that it did not bind appreciably. The heads used in these tests varied from 7.19 to 9.0 pounds in weight and were dropped through distances of 67.88 feet (5 tests) and 79.92 feet (1 test). The measured velocity had a range of variation of 57.4 to 65.6 feet per second (39 to 45 miles/hour). In the 5 tests for which it was determined, the available kinetic energy at the instant of impact varied from 455 to 581 foot pounds. The peak acceleration of the 6 tests ranged from 162 to 724 g and the duration of the acceleration (5 tests) varied from 0.0019 to 0.01125 second.

Three fractures were produced in this series of tests. The first fracture was produced in the head of a white female of unknown age. However, the head bounced off the instrument panel onto the concrete floor so it is impossible to determine just what produced the fracture. Consequently, this particular experiment was considered as "no test."

TABLE III.—GUIDED FALL TESTS OF HUMAN CADAVER HEADS WITH FRAME MODIFIED TO AVOID BINDING

Test	Cadaver data	Head wt., lbs.	Distance dropped, ft.	Computed values			Measured values			Peak acceleration, g ft./sec.²	Total time duration of acceleration, sec.	Remarks
				Velocity, ft./sec.	MPH	Energy, ft. lbs.	Velocity, ft./sec.	MPH	Energy, ft. lbs.			
23	60 W M	7.50	79.92	72.0	49	600				162	0.0019	No fracture. Glancing blow
24	W F	7.19	67.88	66.3	45	488.0	64.9	44	471	337	0.01125	Fracture. Probably from fall on concrete floor. No test
25	60 W M	8.88	67.88	66.3	45	603.0	57.4	39	455	257		No fracture
26	60 W M	9.0	67.88	66.3	45	612.0	64.6	44	581	724	0.00338	Fracture
27	W M	9.0	67.88	66.3	45	612.0	63.3	43	561	344	0.00488	Fracture
28	64 W M	8.6	67.88	66.3	45	587.0	65.6	45	577	686	0.00938	No fracture

F=female; M=male; N=Negro; W=white.

An extensive comminuted and egg-shaped fracture of the parietal bones and the right and left side of the frontal bone (Fig. 6) was produced in the skull of a white man 60 years of age (test 26, Table III). This head, at the instant of impact, had a total available kinetic energy of 581 foot pounds, a velocity of 64.6 feet per second (44 miles/hour), and a peak acceleration of 724 g with a total time duration of 0.00338 second.

The third fracture was produced in the head of a white male of unknown age (test 27, Table III). This was also an extensive, comminuted and depressed fracture of the left parietal bone with a smaller fracture line extending from the left part of the frontal bone superiorly into the parietal of the same side (Fig. 7). At the time of impact the head had 561 foot pounds of kinetic energy available, a velocity of 63.3 feet per second (43 miles/hour) and a peak of acceleration of 344 g which endured for 0.00488 second.

Oscillograph records (Fig. 1). In 14 tests (tests 15–28, Tables II and III) an oscillograph record of the acceleration during impact was obtained from a Statham 500 g capacity accelerometer which was screwed onto the occipital bone of the head. The oscillograph record obtained in 4 of the tests is illustrated in Figure 1.

The first record (test 20) was obtained from the head of a white female of unknown age in which no fracture was produced. The total time duration of the deceleration was 0.018 second, most of it taking place in slightly less than 0.010 second, with the peak deceleration (368 g) reached at approximately 0.002 second.

The second record is an example of the type of record obtained during a fracture (test 13). The total time duration of the deceleration of the head of a Negro man of unknown age was practically the same as in test 20 but the peak deceleration (555 g) was reached slightly sooner (at a little less than 0.002 sec.) than in test 20. In this test most of the deceleration was completed in less than 0.008 second. Thus in test 13 the deceleration occurred in less time than in test 20.

In test 13 the peak deceleration was also reached at approximately 0.002 second. However, the magnitude of this peak deceleration (555 g) was considerably greater than that in test 20 (368 g), which indicates that the rate of the deceleration was greater in test 13 than in test 20.

There were also differences in the total available energy in the two tests. In test 13 the available energy (268 ft. lbs.) was considerably less than the energy of test 20 (338 ft. lbs.) in which no fracture occurred. However, in test 13 the energy was absorbed in a shorter time than in test 20 and the degree of physical damage is a function of the rate of absorption of the energy as well as its magnitude.

TABLE IV.—VARIATIONS IN THE AMOUNTS OF ENERGY AND THE VELOCITY OF DECELERATION IMPACTS APPLIED TO VARIOUS REGIONS OF THE HUMAN CADAVER HEAD

No. of tests	*Site of impact*	*Magnitude of the energy, ft. lbs.*	*Velocity, ft./sec.*
10	Midfrontal region	24.6—66.9	13.5—17.4
17	Anterior inter-parietal region	49.2—75.1	15.2—22.8
9	Occipital region	33.3—45.7	14.7—18.9
10	Posterior parietal region	40.2—75.6	16.4—20.7

Data from Gurdjian, Webster, and Lissner, 1949 (2).

In tests 13 and 20 the peak deceleration occurred slightly before and after 0.002 second, respectively, but a different appearing record was obtained (test 22) in the head of a white male of unknown age. Here most of the deceleration took place between 0.003 and 0.010 second although additional deceleration was seen between 0.010 and 0.018 second. The peak deceleration (527 g) was reached at approximately 0.007 second, and the total time duration was 0.018 second. No fracture was produced.

In test 26 the profile of the record was less serrated than in any of the preceding records. Most of the deceleration took place between 0.003 and 0.007 second, with the peak deceleration (724 g) occurring at 0.004 second. The total time duration of the deceleration was 0.018 second. In this head the fracture was produced and most of the deceleration occurred in approximately 0.004 second, while similar phenomena in test 13 required about 0.007 second. In tests 20 and 22, in which no fractures were produced, the major part of the deceleration occurred in approximately 0.009 and 0.006 second, respectively.

The oscillograph records, as well as the other data obtained from these tests, indicate that the longer the time during which the energy is absorbed or the deceleration occurs the greater the magnitude of the energy or peak deceleration that can be safely tolerated. The importance of this time factor in the mechanics of skull fracture has not been sufficiently appreciated or emphasized in the past.

DISCUSSION

As far as the authors are aware, the only previous studies on the relation of energy, velocity and deceleration to skull fracture are those of Gurdjian, Webster, and Lissner (3). These investigators produced single linear, two linear, and stellate fractures in intact adult human cadaver heads with different amounts of energy applied at varying velocities to various regions of the head. Their results are summarized in Table IV. Their original energy values were given in inch pounds but have been converted into foot pounds for easier comparison with the results which have been obtained in the present study.

From comparison of Table IV with Tables I to III it is seen that Gurdjian, Webster, and Lissner employed considerably less energy, applied at lower velocities, than was used in the present studies. However, the experimental conditions were not the same in the two investigations.

Gurdjian, Webster, and Lissner tested their specimens by dropping them through a relatively short distance (2.8 to 8.0 ft.) upon a solid steel slab weighing 160 pounds. Therefore, because of the relatively small amount of energy and the low velocity, and the difference in mass and density of the head and steel block, there was little, if any, energy transfer between the head and the steel slab. The amount of energy absorbed by the steel slab would be negligible so that most of the available energy was expended in deforming or fracturing the skull.

In the present tests the heads were dropped upon a 1954 Ford instrument panel instead of a solid steel slab. Therefore, because of the relative softness and flexibility of the instrument panel, a large proportion of the available energy of a test was transferred from the head to the panel and was expended in denting and deforming the panel. The test conditions thus much more closely approximate conditions that frequently occur in an automobile accident than did the earlier tests of Gurdjian, Webster, and Lissner (loc. cit.).

FIGS. 2 to 7. The arrows indicate the fracture line. The wire seen in some of the photographs was used to fasten the head to the supporting frame.

FIG. 2. Test 7. Fracture produced in the skull of a white male of unknown age. At the instant of impact the total computed available energy was 318.1 foot pounds and the velocity 52.4 feet per second (36 miles/hour).

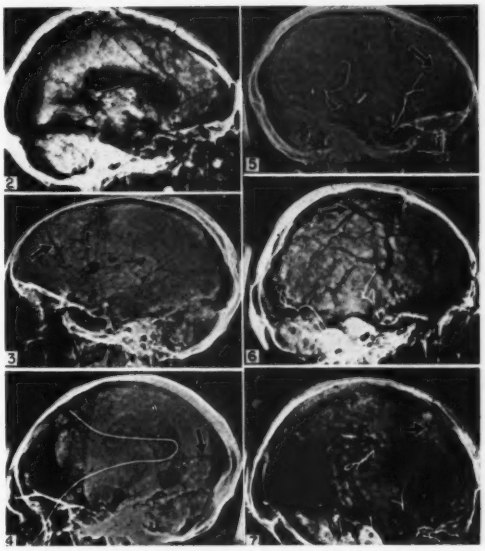
FIG. 3. Test 8. Fracture produced in the skull of a white male 57 years of age. At the instant of impact the total computed available energy was 348.6 foot pounds and the velocity 52.3 feet per second (36 miles/hour).

FIG. 4. Test 12. Fracture produced in the skull of a Negro male of unknown age. At the instant of impact the total computed available kinetic energy was 481.9 foot pounds and the velocity 60 feet per second (41 miles/hour).

FIG. 5. Test 13. Fracture produced in the skull of a Negro male of unknown age. The head, at the instant of impact, had a total available kinetic energy (measured from high speed motion picture film) of 268 foot pounds, a velocity of 48 feet per second (32 miles/hour) and a peak acceleration of 555 g with a total time duration of 0.00903 second.

FIG. 6. Test 26. Fracture produced in the skull of a white male 60 years of age. At the instant of impact this head had a total measured available kinetic energy of 581 foot pounds, a velocity of 64.6 feet per second (44 miles/hour) and a peak acceleration of 724 g with a total time duration of 0.00338 second.

FIG. 7. Test 27. Fracture produced in the skull of a white male of unknown age. At the instant of impact this head had a total measured available kinetic energy of 561 foot pounds, a velocity of 63.3 feet per second (43 miles/hour), and a peak acceleration of 344 g with a total time duration of 0.00488 second.

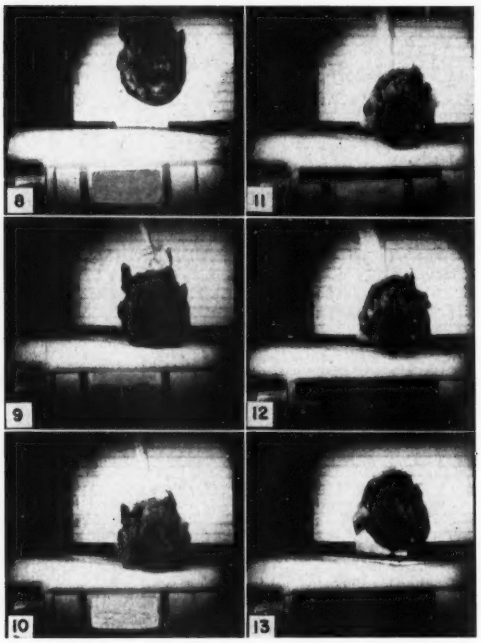


In both series of studies linear fractures were produced. The close similarity between the type of fractures occurring in the present investigation and those in the earlier studies of Gurdjian, Webster, and Lissner suggests that the actual amount of energy responsible for the fractures was approximately the same (33 to 75 ft.lb.) in both types of tests. The remainder, and larger proportion, of the available energy of the present tests was spent in deforming the instrument panel.

When evaluating the damage produced by a blow not only the magnitude of the energy involved but its rate of absorption must be considered. Other things being equal, a greater amount of energy can be safely tolerated if it is absorbed slowly than if it is absorbed rapidly.

In tests 22 and 28, in which peak decelerations of 527 g and 686 g were reached, the energy was absorbed in 0.006 and 0.009 second, respectively, without fracture occurring. However, in test 13, in which a peak deceleration of 555 g was reached, the energy was absorbed in 0.009 second and produced a fracture. In tests 26 and 27 peak decelerations of 724 g and 344 g were reached and also resulted in fractures. But the total time duration of the deceleration, during which the available energy was absorbed, was only 0.003 and 0.004 second, respectively. However, the time during which the energy is absorbed is not the only factor since biologic considerations such as the thickness of the scalp and the skull, the age of the individual, the state of health, and possibly sex and race, are also involved. The exact point of application of the force to the head, as well as the site of impact on the panel, must also be considered in evaluating the results of a test.

Gurdjian, Lissner, and associates (2) also investigated the peak acceleration of the skull, with reference to concussion and fracture, in living anesthetized dogs. The acceleration of the skull was produced by striking it with ball peen hammers of various weights. In 20 dogs linear, depressed, or comminuted fractures were produced by accelerations varying from 190 to an estimated 780 g.



FIGS. 8 to 13. Photographic record, selected from a high speed (1000 frames/second) motion picture film, of the behavior of a head just before, during, and after the instant of impact. Test No. 7, weight of head 7.5 pounds. The fracture produced during this test is seen in Figure 2.

FIG. 8. The head just before impact.

FIGS. 9 and 10. The head during impact. Note the deformation and dent produced in the instrument panel.

FIGS. 11 to 13. The head rebounding from the instrument panel. Note that the door to the glove compartment, just below the head, has been forced open by the impact.

The intracranial pressure rise measured at the same time varied from 25 to 95 pounds per square inch. The magnitude of this pressure rise can be better appreciated when it is remembered that 50 pounds per square inch corresponds approximately to 2,600 millimeters of mercury.

The accelerations in their investigations were of a range of magnitude and variation similar to the peak decelerations measured in the present tests. However, their tests corresponded to the first of the possible conditions, i.e., the resting head, which is free to move, is struck by a moving object and thus accelerated, whereas the present tests fulfilled the second condition in which the moving head strikes a resting object and is decelerated.

SUMMARY

1. Twenty-eight tests, 10 free fall and 18 guided fall, were made by dropping, through varying distances, embalmed adult human cadaver heads upon a 1954 Ford instrument panel.

2. The available kinetic energy and the velocity, computed from theory, of the heads at impact in the free fall tests varied from 32.5 to 52.5 feet per second and from 134 to 426.7 foot pounds, respectively.

3. The measured available kinetic energy and the velocity of the heads at impact in the first series of guided fall tests, made with the original apparatus, ranged from 268 to 473 foot pounds and from 43.5 to 59.2 feet per second, respectively. The measured peak acceleration varied from 180 to 724 g with a duration varying from 0.0075 to 0.0117 second.

4. In a second series of guided fall tests, using the apparatus modified to avoid binding, the heads at impact had a measured available kinetic energy varying from 471 to 581 foot pounds, a velocity of 57.4 to 64.9 feet per second, and a peak acceleration of 162 to 724 g with a duration which ranged from 0.0019 to 0.01125 second.

5. Linear or comminuted fractures of the skull were produced with impact velocities of 43 feet per second (29 miles/hour) to 65 feet per second (45 miles/hour). The total available kinetic energy at impact varied from 268 to 581 foot pounds.

6. Fractures occurred with peak impact accelerations of 337, 344, 555, and 724 g, having total time durations of 0.01125, 0.00488, 0.00903, and 0.00338 second, respectively.

7. The embalmed adult human head can tolerate, without fracture, peak impact accelerations as high as 686 g and available kinetic energy as great as 577 foot pounds.

8. The magnitude of the energy producing skull fracture is approximately 33 to 75

foot pounds, the major portion of the kinetic energy available in a test being used in denting and deforming the instrument panel upon which the head has been dropped.

9. The results of the tests in which the total time duration of the peak acceleration was measured indicate that not only the magnitude of the available kinetic energy but also its rate of absorption is important in the mechanism of skull fracture. Thus, the longer the time for the absorption of the energy the greater the magnitude of the energy that can be safely tolerated.

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A SYNDROME OF CONGENITAL DEFECTS INVOLVING THE ABDOMINAL WALL, STERNUM, DIAPHRAGM, PERICARDIUM, AND HEART

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DURING RECENT YEARS, several patients with an unusual combination of congenital defects have been seen in The Johns Hopkins Hospital. The anomalies observed in each patient were: (1) a midline, supraumbilical abdominal wall defect; (2) a defect of the lower sternum; (3) a deficiency of the anterior diaphragm; (4) a defect in the diaphragmatic pericardium; (5) congenital intracardiac defects. The repeated association of these abnormalities suggested that this combination represented a clinical syndrome and stimulated a search for additional examples. This article was written to summarize the available clinical material, to propose a probable embryologic basis for the coexistence of these defects, and to consider the surgical treatment of patients with this syndrome.

CASE REPORTS

CASE 1. C. D., a male infant, was delivered at The Johns Hopkins Hospital by Dr. W. Drummond Eaton on February 8, 1957. In the family history there were no other instances of congenital defects. This was his mother's first pregnancy, during which there had been no recognized infections or unusual environmental exposures. Delivery was uncomplicated, birth weight was 3,170 grams. A large omphalocele was immediately apparent (Fig. 1), and it was further noted that the cardiac pulsations were abnormally prominent. The sternum was shortened and the costal arch was elevated and flared. The contour of the heart was visible beneath the skin of the unusually high epigastrium. There was a defect of the musculature of the abdominal wall above the omphalocele; the medial edges of the rectus muscles were widely separated and inserted on the costal margins at the midclavicular line. The child appeared otherwise normal. No cardiac murmurs were audible.

The child was operated upon (J.R.C.) under vinethene-ether anesthesia. The amniotic sac was excised with a small margin of skin (Fig. 2). The liver, which occupied the upper portion of the omphalocele, could then be depressed to reveal a large defect in the ventral portion of the diaphragm (Fig. 3A). The diaphragm arose normally from the posterior and lateral aspects of the rib cage but at a point in line with the insertion of the rectus muscles on the costal margins the diaphragm curved posteriorly, leaving a semilunar defect which was bounded dorsally by a small cuff of diaphragm on the liver immediately ventral to the inferior vena cava. There was a corresponding defect in the pericardium. The serous linings of the peritoneal and pericardial cavities were continuous across the edge of the diaphragmatic defect. The pleurae were intact. The heart lay somewhat further to the right than normal, and there was an anomalous anterior coronary artery. In the abdomen there was failure of attachment of the mesentery of the small bowel and right colon. The cecum lay in the epigastrium, and the appendix lay within the pericardial cavity.

Attention was first directed to closure of the diaphragmatic defect. The junction of pericardium and peritoneum was incised along the edge of the diaphragmatic defect and the pericardium reflected from the diaphragm. The edge of the diaphragm was then sutured to the anterior rib cage (Fig. 3B). It was apparent that the rectus muscles could not be approximated. It was possible, however, to develop a layer of fascia which was continuous with the medial border of the rectus sheath and had the appearance of linea alba (Figs. 4 and 5). The edges of this fascia were brought together in the midline after a long relaxing incision had been made in each anterior rectus sheath.

The child recovered satisfactorily but during his convalescence a murmur was noted over the left second interspace. Mild congestive failure developed which required digitalization. Radiologic study

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demonstrated a large right ventricle and an electrocardiogram revealed right ventricular hypertrophy. A presumptive diagnosis of tetralogy of Fallot was made although cyanosis was not apparent. He was discharged in satisfactory condition at 3 weeks of age.

He was readmitted at 3 months of age because of large symptomatic indirect inguinal hernias. The pulmonary systolic murmur was again noted and cyanosis was detected on crying. The abdominal wall repair was intact (Fig. 6). His weight gain and development were approximately normal. The hernias were repaired without event. He has continued to develop normally although there is slight cyanosis on vigorous crying. Subsequent angiocardiography has substantiated the diagnosis of tetralogy of Fallot. Correction of the cardiac defects has been deferred until the child is older.

CASE 2. M. F. was first seen in the Cardiac Clinic in 1948 at the age of 16 years. He was the second of 3 siblings. Absence of the lower third of the sternum and a large defect of the abdominal musculature above the umbilicus were noted at birth. Cyanosis was first detected at 2½ years and a cardiac murmur was heard at that time. He subsequently developed shortness of breath, increasing cyanosis, and marked diminution of exercise tolerance.

On physical examination, the patient was noted to be small and poorly nourished. There was an 8 by 10 centimeter defect of the musculature of the abdominal wall above the umbilicus (Fig. 7). The rectus muscles inserted into the costal margins at the midclavicular line. The lower sternum was absent and only 4 ribs joined the remaining portion. The defect was covered by hyperpigmented skin with little if any subcutaneous tissue. The contours of the heart, liver, and intestines were visible in the defect. No murmurs could be heard although cyanosis and clubbing of the extremities were marked. The physical examination was otherwise normal.

The hematocrit was 76, and an electrocardiogram revealed right axis deviation and right ventricular hypertrophy. Fluoroscopy revealed dextrorotation of the heart and a left aortic arch. Cardiac catheterization and angiocardiographic studies demonstrated a functional single ventricle and pulmonic stenosis.

On May 1, 1948 an anastomosis was performed between the end of the right subclavian and the side of the right pulmonary artery by Dr. William P. Longmire. After operation a loud, continuous murmur was audible and cyanosis was strikingly diminished.

The patient returned for study 4 years later. He was at that time a college student and reported that he was no longer cyanotic except on extreme exertion. There was no visible cyanosis, and the loud continuous murmur was again noted. The abdominal wall defect was unchanged.

On May 29, 1952, repair of the ventral defect was carried out (M.M.R.). The defect was found to be

Fig. 1. Case 1. Photograph taken immediately after birth showing the omphalocele and the abnormal costal arch.

covered only by skin and peritoneum. When the liver had been reflected downward, one could visualize a large semilunar defect in the anterior diaphragm with a corresponding defect in the diaphragmatic pericardium (Fig. 8). The pericardium was adherent to the heart at the margin of this defect. There was no defect in the pleurae. With dissection of the pericardium from the pleurae, diaphragm, and epicardium (Fig. 9) the heart retracted into the thorax although the apex remained visible in the epigastric defect. It was impossible to approximate the rectus muscles. Long incisions were made in the anterior rectus sheaths, and the medial fascial flaps were reflected to the midline where they were sutured (Fig. 10A). This closure was reinforced by a sheet of autogenous fascia lata (Fig. 10B). An excellent result has been noted on subsequent examinations.

CASE 3. R. B., a little boy, was first seen in The Johns Hopkins Hospital at the age of 2 years. This was his mother's first pregnancy, during which there had been no recognized illnesses or unusual environmental factors. There was no history of congenital defects in the family. The child was noted at birth to have a defect of the sternum and a cardiac murmur. Subsequently, increasing cyanosis and limitation of activity had developed.

Physical examination revealed a well developed child with generalized cyanosis and marked clubbing of the fingers. The lower half of the sternum was absent. This anomaly and an associated wide separation of the rectus muscles above the umbilicus pro-

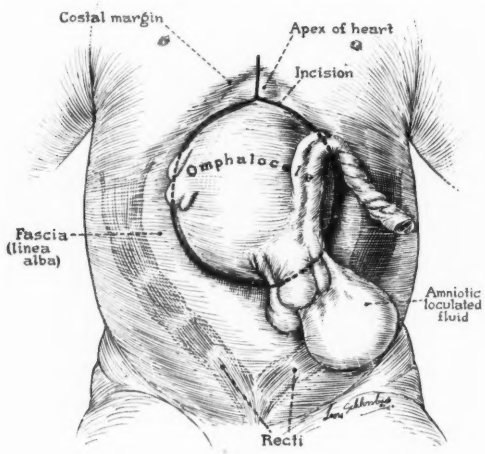
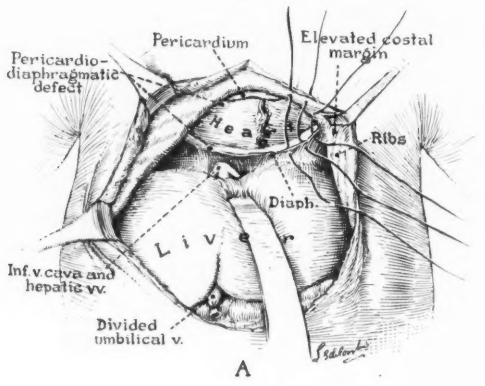


FIG. 2.



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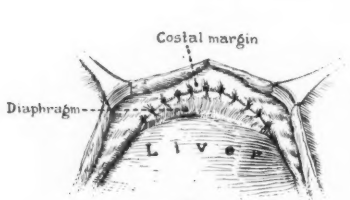

B

FIG. 3.

FIG. 2. Case 1. Note the wide separation of the rectus muscles which is present, the abnormalities of the sternum and rib cage, and also the exposed position of the heart.

FIG. 3. Case 1. Note the defects of the diaphragm, pericardium, and thorax, and the repair of the diaphragmatic defect.

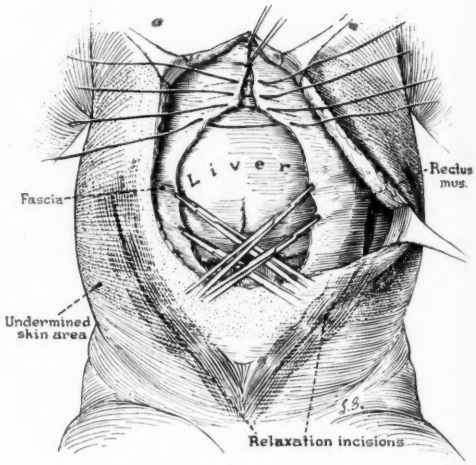

FIG. 4.

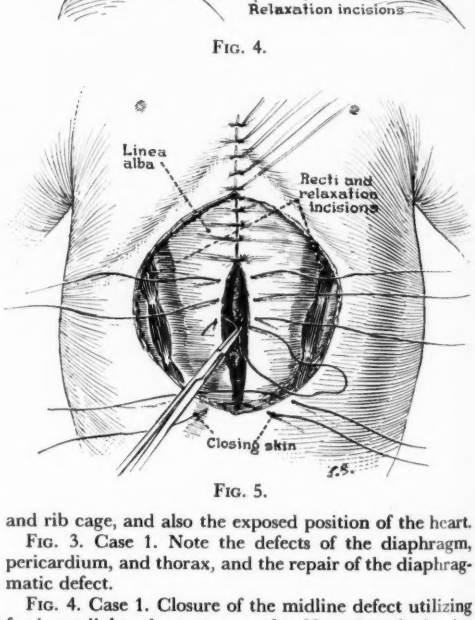

FIG. 5.

FIG. 4. Case 1. Closure of the midline defect utilizing fascia medial to the rectus muscles. Note the relaxing incisions in the anterior rectus sheath and lateral undermining of the skin.

FIG. 5. Case 1. Completed closure, illustrating adequate repair of the defect despite the lateral position of the rectus muscles.

duced a large thoracoepigastric defect in which the apex of the heart was palpable beneath the skin. A harsh systolic murmur was audible over the entire precordium, maximal in the second intercostal space.

The hematocrit was 46. An electrocardiogram showed right axis deviation and right ventricular hypertrophy. Fluoroscopy revealed dextrorotation of the heart and a left aortic arch. An angiocardiogram showed marked overriding of the aorta, an interventricular septal defect, and pulmonic stenosis.

It was thought that this patient represented a typical tetralogy of Fallot, and on July 2, 1957 a right subclavian-pulmonary anastomosis was performed (J.A.H.). The clinical response was excellent

and the child was discharged from the hospital much improved (Fig. 11). He is to return for repair of the other defects.

CASE 4. R. K., a 6 weeks old white male, was admitted to The Johns Hopkins Hospital in 1952 because of an upper abdominal defect which had been present since birth. This was his mother's only pregnancy. There was no history of congenital defects in the family nor had there been any significant diseases or unusual environmental factors during the mother's pregnancy. Delivery was said to be uncomplicated but a large upper abdominal defect was immediately apparent. No other anomalies were noted. Progress was satisfactory except for a single episode of cyanosis on vigorous crying at 3 weeks of age.

Physical examination on admission revealed a well nourished infant who had an obvious defect in the ventral body wall (Fig. 12). The sternum was shortened and a 9 by 5 centimeter defect was noted in the upper abdomen with wide separation of the rectus muscles. A pulsatile structure extending to the umbilicus was palpable within the defect. Its relation to the heart could not be determined. The heart was enlarged to the right, and there was a loud systolic murmur, maximal in the right fourth intercostal space. The child was not cyanotic.

Hematologic studies were unremarkable. X-ray examination and fluoroscopy of the chest revealed cardiac enlargement. An electrocardiogram revealed a balanced axis. Angiocardiography showed dextrorotation of the heart, an interventricular septal defect, and a diverticulum arising from the left ventricle.

Excision of this diverticulum was attempted but cardiac arrest occurred shortly after the skin incision was made and the patient expired.

A limited postmortem examination did not define the nature of the sternal defect. There was a dilated right atrium and hypertrophy of the right ventricle. The foramen ovale was patent. There was a 5 millimeter patent ductus arteriosus and a persistent left superior vena cava which entered the coronary sinus. A high interventricular septal defect measuring 2.5 centimeters in diameter was noted. The left ventricle was of normal size but from the apex of this ventricle arose a diverticulum which extended downward subcutaneously for a distance of 6.5 centimeters. The lumen of this diverticulum was 4 millimeters in diameter and was lined by endocardium. There were defects of the pericardium and ventral diaphragm through which the diverticulum passed. The diaphragmatic defect was semilunar in shape with the dorsal margin of the defect at the point of fusion of diaphragm and liver. The diaphragm joined the rib cage on either side at the midclavicular line.

CASE 5. A. S., a 5 months old white female, was admitted in 1952 because of cyanosis and episodes of unconsciousness. There were no congenital defects in the family history. This was the mother's first pregnancy, during which there had been no recognizable viral infections or unusual environmental exposures. The child was delivered at another hospital in a breech presentation and was immediately noted to be cyanotic with a loud systolic murmur over the base of the heart. She was also found to have an omphalocele. Hospital records reveal that the omphalocele was repaired several hours after birth at which time a "pulsatile, bluish, pointed structure," thought to be the apex of the heart, was observed and was "pushed back into the chest cavity." Recovery from this operation was satisfactory but the child became increasingly cyanotic. At 4 months of age she began to have episodes of intense cyanosis associated with rigidity, opisthotonos, and unconsciousness.

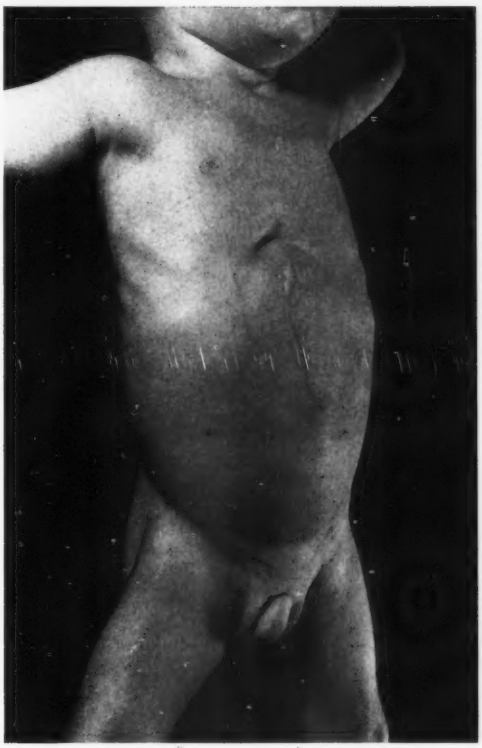

FIG. 6. Case 1. Photograph taken at 3 months showing the abdominal wall repair and the defect of the costal margin and sternum. Bilateral inguinal hernias have been repaired.

At the time of her admission to this hospital, she was malnourished and cyanotic with clubbing of the extremities. A loud systolic murmur was heard over the base of the heart, maximal in the left second and third intercostal spaces adjacent to the sternum. There was wide separation of the rectus muscles which inserted into the costal margins at the midclavicular

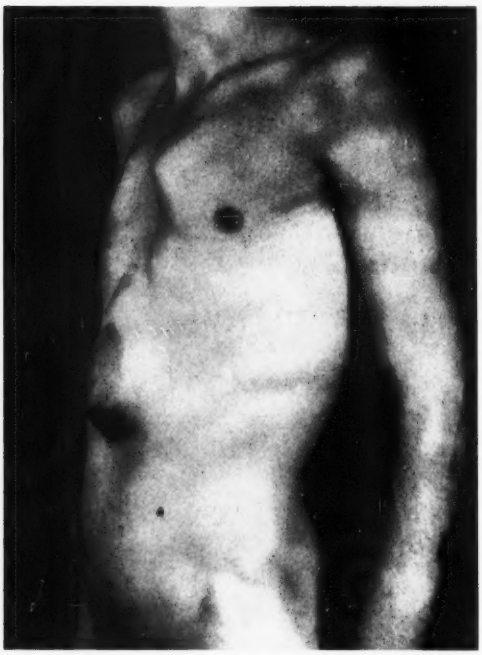

FIG. 7. Case 2. Preoperative photograph revealing the defects of the thorax and abdominal wall.

line. It was thought that the xiphoid was missing and a pulsatile mass was noted beneath the skin of the abdominal wall defect.

The hematocrit was 60. Arterial oxygen saturation was 45 per cent with the child crying. An electrocardiogram revealed slight left axis deviation. Fluoroscopy revealed enlargement of the heart with marked prominence of the right cardiac border. There was a left aortic arch.

A diagnosis of tricuspid atresia was made and, because of the severity of symptoms, the child was operated upon shortly after admission to the hospital. Cardiac arrest occurred soon after the chest was entered but resuscitation was successful and a subclavian-pulmonary arterial anastomosis was constructed. The child did poorly, however, and died several hours postoperatively.

At autopsy, an upper abdominal wall defect was noted with wide separation of the rectus muscles which inserted into the costal margins at the midclavicular line. A diverticulum of the left ventricle extended through a ventral defect in the diaphragm and a corresponding defect in the diaphragmatic pericardium. This diverticulum arose from the apex of the ventricle and extended about 2 centimeters below the diaphragm. A persistent left superior vena cava entered the coronary sinus. There was a large interatrial septal defect and a high interventricular septal defect. A common pulmonary vein was found to drain both lungs into the left auricle. The tricuspid valve was atretic. There was a single coronary artery.

CLINICAL ANALYSIS

Previously, patients with this combination of anomalies have been considered to be examples of ectopia cordis because of the abnormally exposed position of the heart. The signal articles bearing upon this subject are those of Greig, Byron, and Major. Greig summarized the earlier reports of ectopia cordis but did not analyze associated anomalies. Byron first suggested a distinction between the other categories of ectopia cordis and those associated with abdominal wall defects; he proposed that the latter be segregated as a subgroup under the term thoracoabdominal. Major has more recently presented a review of this type in which he quoted 13 cases and added a case of his own.

The clinical data available on the previously reported patients are summarized in Table I and those on the patients herein reported in Table II. Analysis of this material reveals several facts previously unrecognized: (1) Rather than a single abnormality, these patients present a remarkably consistent association of defects which includes anomalies of the abdominal wall, lower sternum, ventral diaphragm, pericardium, and heart. (2) The ventral diaphragmatic defect is a specific anomaly unrelated to the commonly recognized diaphragmatic defects. (3) Intracardiac anomalies are invariably present. (4) True ectopia of the heart is rare, occurring in but 1 patient of the entire group. Except for some degree of dextrorotation which may be present, the heart usually lies in normal relationship to the other thoracic viscera; the appearance of ectopia is created by the concomitant defects of the sternum, diaphragm, and abdominal wall which leave the heart abnormally exposed.

On the basis of these observations, the inclusion of these patients in the category of

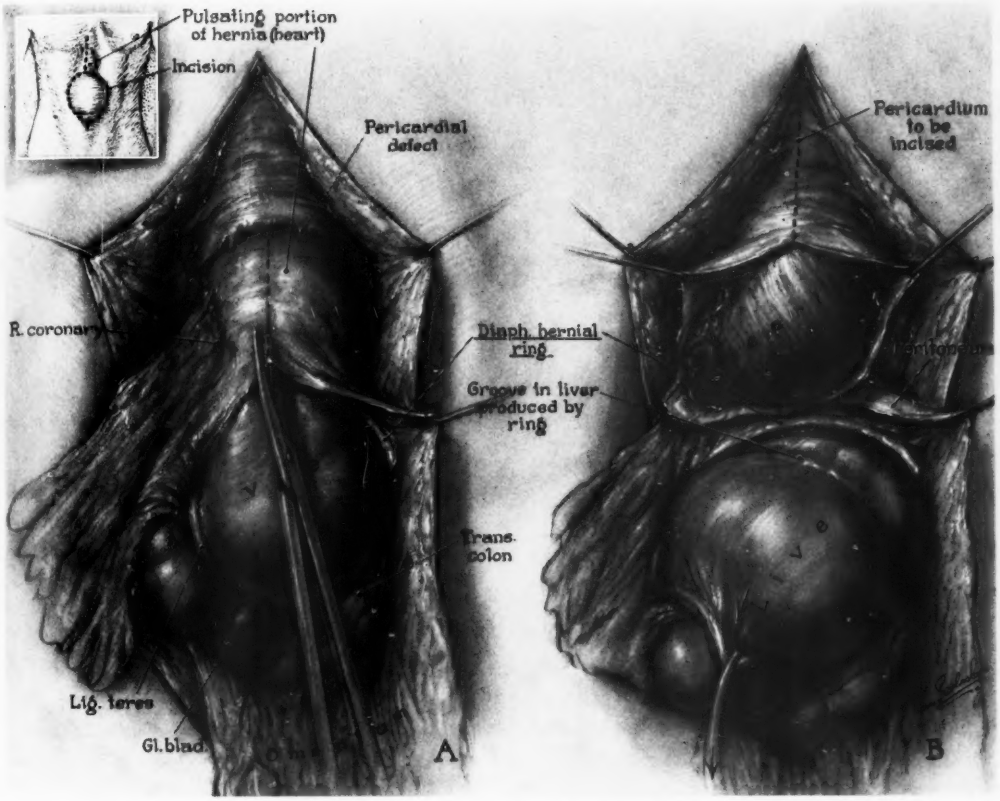

FIG. 8. Case 2. Note the exposed position of the heart produced by the sternal and abdominal wall defects and the diaphragmatic and pericardial defects.

ectopia cordis would appear to be in error. Rather, this consistent association of anomalies should be considered as a specific syndrome.

Variants of this syndrome would be anticipated in view of the postulated embryologic development of these defects. Potts has reported a patient who demonstrated cardiac, abdominal wall, and diaphragmatic defects but had a normal sternum and an intact though abnormal pericardium. Major has successfully treated a newborn infant who had an omphalocele, a defect of the sternum and lower thorax, and a ventral defect of the diaphragm without an associated pericardial defect and no clinically apparent intracardiac anomalies. These are obviously closely related conditions and may be explained on the basis of less extensive embryologic defects. While most of the component elements of this syndrome may occur as isolated anomalies, the ventral diaphragmatic defect probably will not be found in the absence of concomitant defects of the sternum and abdominal wall. It should be emphasized that this anomaly is not related to foramen of Morgagni defects but is embryologically a separate entity.

The occurrence of congenital intracardiac anomalies as a constant element of this complex has not been previously recognized. It would appear from the present study that such lesions should be considered an integral part of this association. An analysis of these

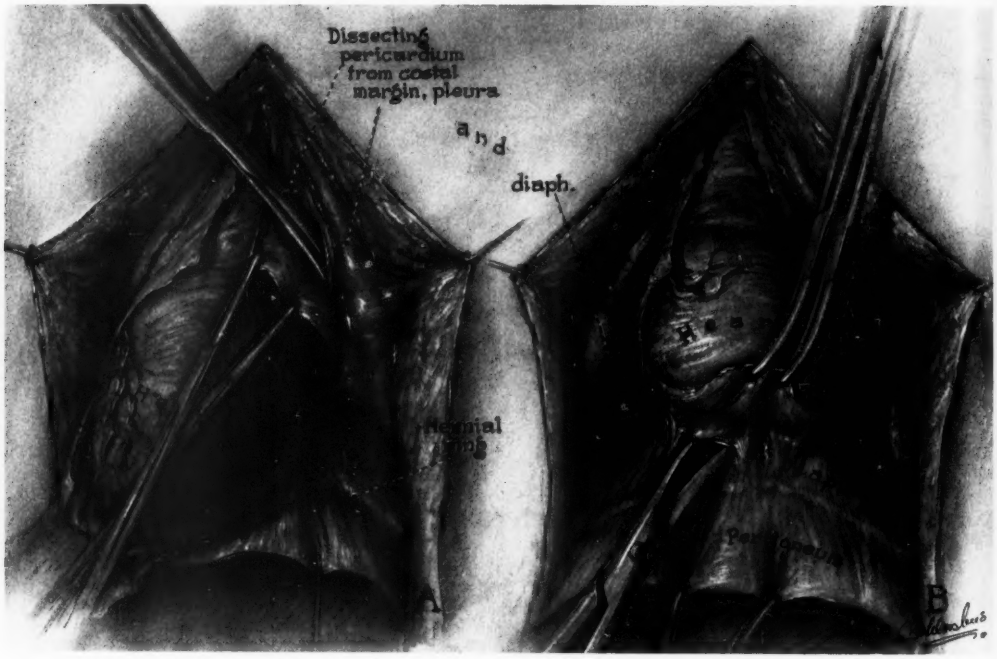

FIG. 9. Case 2. Dissection of heart and pericardium from surrounding structures allows the heart to retract somewhat within the thoracic cavity.

cardiac defects (Table III) reveals that an interventricular septal defect was present in every instance in which a description of the heart was available. An interatrial septal defect was present in 53 per cent of the patients. Either valvular or infundibular pulmonary stenosis occurred in 33 per cent of the patients. The only established cardiac syndrome to be noted with any frequency was the tetralogy of Fallot which was seen in 20 per cent of the patients. A left ventricular diverticulum was present in 20 per cent.

It is of clinical importance that only 4 of the entire group of patients had other significant congenital defects, and but 1 of these was incompatible with life. In only 3 patients were the total anomalies such as to preclude successful correction.

EMBRYOLOGIC DEVELOPMENT

Normal embryology. An analysis of the normal embryology of the involved structures is essential to clarification of the relationship of these associated anomalies.

Origin of the mesoderm.—During the eighth day of embryonic development, a layer of cells differentiates from the inner surface of the inner cell mass and pushes out into the blastomere; this is the primitive entoderm which will eventually form the lining of the gut. Immediately thereafter, a localized proliferation of cells is noted on the inner surface of the embryonic disc and migrates laterally between the trophoblast and entoderm; this is the primitive mesoderm. These cells migrate rapidly in a peripheral fashion so that the mesodermal layer soon extends not only beneath the embryo but also lines the entire blastodermic vesicle. At about 16 days the mesoderm splits laterally into an outer somatic layer and an inner splanchnic layer (Fig. 13). The cavity between these layers is the primitive coelom. This somatic-splanchnic differentiation does not occur everywhere simultaneously; it is significant that it appears first in the mesodermal tissue from which the heart and pericardium will develop.

Development of the heart and pericardium.—The heart arises far cephalad from paired primordia which are brought together beneath the embryo at about the

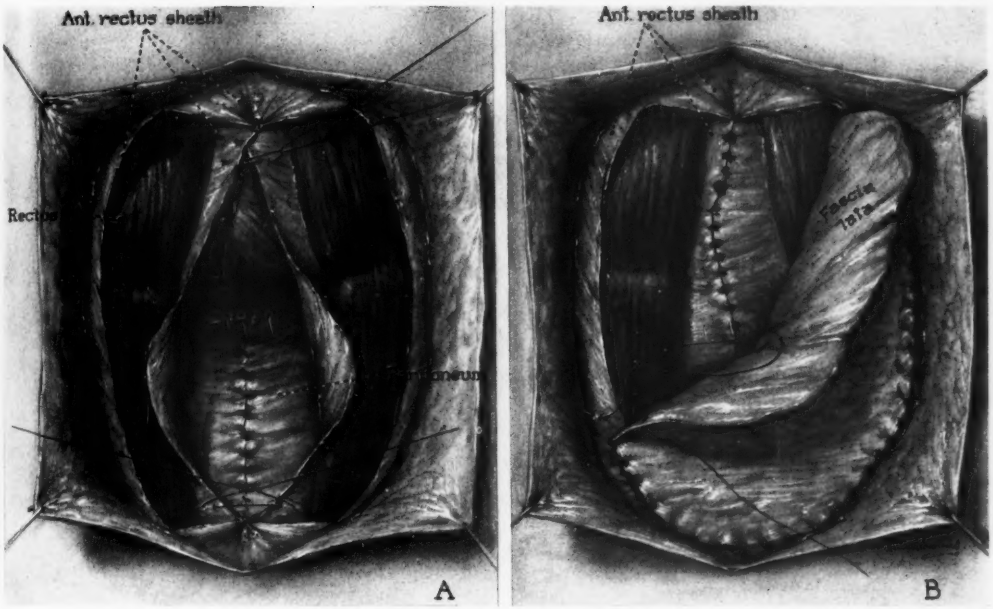

FIG. 10. Case 2. Fascial closure is effected by reflecting flaps of anterior rectus sheath to the midline. Closure reinforced by autogenous fascia lata.

seventeenth day by the downfolding of the lateral splanchnopleure and ventral flexion of the embryo. This ventral folding appears first in the cephalic and caudal portions of the embryo so that the heart reaches its definitive position and begins its differentiation very early in embryonic life (Fig. 13). The myocardium and epicardium are derived from the splanchnic layer of mesoderm while the pericardium arises from the corresponding somatic mesoderm. The intimate developmental relationship of these structures is apparent.

Development of the diaphragm.—From the mesoderm adjacent and immediately anterior to the cardiac primordia arises the transverse septum. This tissue comes to lie in the midline just caudad to the heart by the same process of flexion and ventral folding and is the anlage of the ventral portion of the diaphragm (Fig. 14). The transverse septum develops contemporaneously with and in close proximity to the heart and pericardium and is derived from the same primitive layer. The dorsal and lateral portions of the diaphragm are derived from the pleuropericardial and pleuroperitoneal folds which coalesce with the transverse septum.

Development of the abdominal wall.—It is thought that the somatic mesoderm contributes primarily to the subcutaneous connective tissue of the anterior abdominal wall. The muscular components are derived from the dorsal mesoderm of the somites. The dorsomesial portion of each somite proliferates and extends around toward the ventral midline; termed the myotome, this tissue splits to form the various muscle layers. The skin of the ventral body wall is derived from the embryonic ectoderm which is continuous with the amnion. The development of the skin is not closely related to that of the muscles.

Development of the sternum.—The sternum is formed from paired lateral concentrations of mesenchymal cells in the thoracic region of the embryo (Fig. 15). These cannot be clearly identified prior to the fifth week but the primitive mesoderm from which they are derived is obviously laid down at a much earlier date. They are converted into precartilage and advance toward the midline where they fuse into a single structure. The process of fusion begins at the cephalic end and progresses caudally. Simultaneously, rib cartilages are growing ventrally from the vertebrae and by the ninth week the sternum is complete and the anterior rib ends have become attached.

Development of the specific defects. The anomalies seen in this syndrome may be classified into two groups based on the mechanism of embryologic development. The first group, comprising 3 of the defects, would appear to arise as the result of developmental failure of a segment of the mesoderm.

TABLE I.—ANALYSIS OF DEFECTS NOTED IN PREVIOUSLY REPORTED PATIENTS

	Sternal	*Abdominal wall*	*Diaphragmatic*	*Cardiac*	*Pericardial*	*Other*
Prochaska (1734)	Lower ⅓	Eventration	Ventral defect	?	+	Anencephaly
Pinelli	Lower ⅔	Omphalocele	+	?	?	Absent left lung
Sandifort (1772)	?	Omphalocele	Ventral defect	IASD, IVSD	+	None
Wilson (1798)	Xiphoid	Omphalocele	Ventral defect	IASD, IVSD	?	None
O'Connor (1861)	Lower ⅓	Omphalocele	Ventral defect	+	+	None
Francois-Franck (1877)	Lower ⅓	Eventration	Ventral defect	?	?	None
Holt (1897)	?	Omphalocele	Ventral defect	Tetralogy of Fallot	?	None
Abbott (1898)	Lower ⅓	Diastasis with eventration	Ventral defect	?	?	None
Greifenberg (1908)	Xiphoid	Eventration	?	IVSD	+	None
Foy (1909)	Lower ½	Diastasis	Ventral defect	IASD, IVSD, left SVC	+	None
Welch (1910)	Lower ½	Diastasis with hernia	Ventral defect	?	?	None
Holmes (1919)	Lower ⅓	Diastasis with hernia	Ventral defect	IASD, IVSD	+	None
Blatt and Zeldes (1941)	Xiphoid	Ventral hernia	Ventral defect	IASD, IVSD, tricuspid atresia	?	None
Byron (1948)	Bifid sternum	Omphalocele	?	Tetralogy of Fallot, ectopia cordis	+	Malrotation intestines
Ehrenhaft	+	Diastasis with hernia	Ventral defect	Diverticulum left ventricle, IASD, IVSD, truncus arteriosus, pulmonary stenosis	+	None
Johnson	+	Diastasis with hernia	+	IVSD, PDA	+	None

TABLE II.—ANALYSIS OF DEFECTS NOTED IN PRESENTLY REPORTED PATIENTS

	Sternal	*Abdominal wall*	*Diaphragmatic*	*Cardiac*	*Pericardial*	*Other*
1. C.D.	Lower ⅓	Omphalocele	Ventral defect	Tetralogy of Fallot	+	Malrotation intestines
2. M.F.	Lower ½	Diastasis with hernia	Ventral defect	IASD, IVSD, pulmonary stenosis	+	None
3. J.B.	Lower ⅓	Diastasis with hernia	+	IASD, IVSD, pulmonary stenosis	?	None
4. R.K.	Xiphoid	Diastasis with hernia	Ventral defect	IASD, IVSD, PDA, diverticulum left ventricle	+	None
5. A.S.	+	Omphalocele	Ventral defect	IASD, IVSD, diverticulum left ventricle	+	None

The diaphragmatic defect results from total or partial failure of the transverse septum to develop. When complete, the defect corresponds exactly to that portion of the definitive diaphragm which is derived from the transverse septum; it is a ventral defect extending laterally to the region of the pleuroperitoneal folds and dorsally to the point of attachment of liver and diaphragm (Fig. 14). Less extensive defects represent partial rather than total loss of the transverse septum. This anomaly is not related to defects of the foramen of Morgagni.

The pericardial defect is closely related to faulty development of the transverse septum. That portion of the pericardium which is to lie on the diaphragm arises from the somatic mesoderm immediately adjacent to that region of the same layer from which the transverse septum is derived. Defective development of one of these structures without a corresponding defect in the other requires a highly specific loss of somatic mesoderm and is seen only in the uncommon variants in which the diaphragmatic defect is incomplete. Coexisting defects are much more probable and are seen in the great majority of patients.

The intracardiac lesions noted are the result of faulty development of the epimyocardium which is derived from the splanchnic mesoderm corresponding to that portion of the somatic mesoderm from which the pericardium is derived. The cardiac anomalies

FIG. 11. Case 3. Photograph taken after right subclavian-pulmonary arterial anastomosis showing the defective sternum and rib cage and separation of the rectus muscles. Note that the separation is not as wide as in the other patients and the midline weakness is not as great.

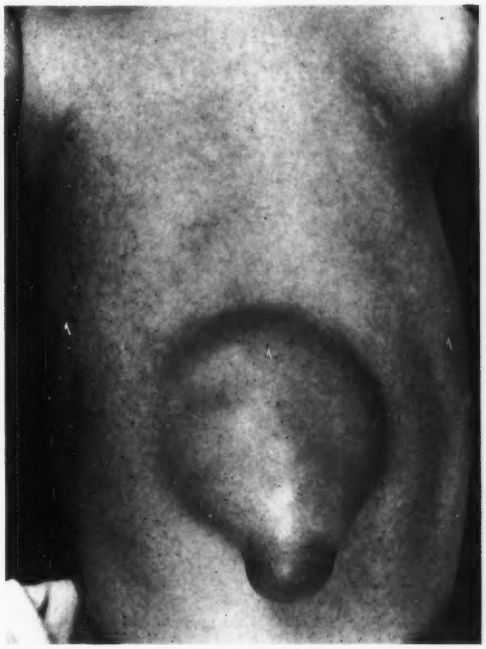

FIG. 12. Case 4. Photograph showing the abdominal wall defect.

demonstrated in these patients are varied but it is striking that in all patients adequately described, defects of the cardiac septa were present. The exact origin of the individual cardiac structures from the primordial tissues is not defined but the consistency of septal defects in these patients might provide a clue to the derivation of these structures.

The second group includes the sternal and abdominal wall defects. These also appear to arise as the result of failure of the normal development of the mesodermal components but would seem to evolve by a somewhat different mechanism than that described for the diaphragmatic, pericardial and intracardiac anomalies.

The sternal defect results from failure of complete ventral migration of the paired primordial structures. It is important to realize that all of the elements of the sternum are present but lie in a position lateral to their normal midline location. The costal cartilages connect with cartilaginous plates which represent the paired sternal anlagen and, in most instances, variable degrees of fusion occur in the more cephalic portion of the thorax. The defect, therefore, does not represent absence of the sternal primordia but rather failure of the paired primitive structures to complete migration.

The abdominal wall defect arises in similar fashion. Here, also, the defect is due not to absence of the normal elements of the ventral abdominal wall but to a failure of complete ventral migration of the myotomes in this region so that normal differentiation into the various muscle layers occurs at an abnormally lateral point. This is illustrated in these patients by the structurally normal rectus muscles which attach correctly to the pubis but deviate laterally as they run cephalad so that they insert into the costal margin at the midclavicular line.

At least two theories may be proposed to explain the failure of ventral migration of the sternal anlagen and of the myotomes: (1) The existence of a primary defect in the growth potential of the migrating tissues. (2) An absence or deficiency of ventral paramidline mesenchymal tissue into which the migrating structures would normally grow. The first possibility seems unlikely in view of the otherwise normal development and differentiation of these tissues. The second alternative is the more attractive since it postulates a developmental defect which is basically similar to that proposed for the associated anomalies of the diaphragm, pericardium, and heart, i.e., absence or

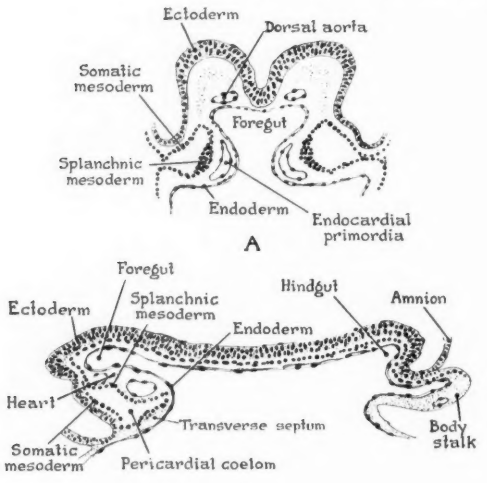

FIG. 13. A, Diagrammatic reconstruction of cross section of human embryo at about 16 days just after differentiation of the mesoderm into somatic and splanchnic layers. B, Longitudinal section at about 17 days after the cardiac anlagen have fused. Note the intimate relation of the developing pericardium and transverse septum.

defective development of the paramidline mesoderm. While the mechanism is therefore different in the two groups, it would appear probable that the basic defect is identical.

This explanation demands that the development of the mesoderm be altered at a very early period in embryonic life. The abnormality must occur prior to or immediately after the differentiation of the primitive intraembryonic mesoderm into its splanchnic and somatic layers since derivatives of both these layers are involved. This localizes the time of origin at about 14 to 18 days of embryonic life. The basic etiology of this mesodermal maldevelopment remains obscure.

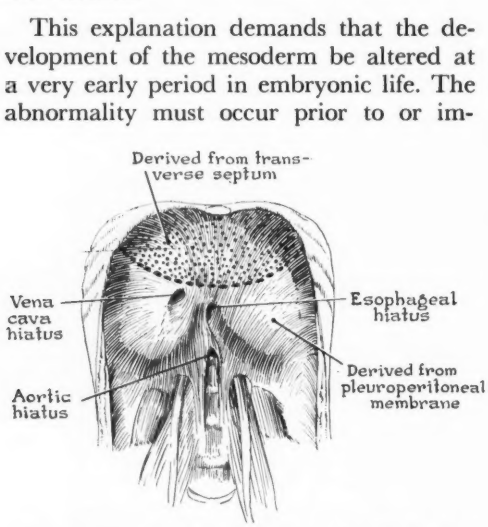

FIG. 14. The adult diaphragm, indicating the embryologic origin of the various portions. Note the similarity between the portion derived from the transverse septum and the defect noted in this syndrome.

TREATMENT

In view of the multiplicity of problems posed by these patients, it is not practical to formulate a specific plan of attack which will be optimal for all patients but, in general, treatment should consist of immediate surgical correction of as many of the defects as possible. Repair of the cardiac lesions should be deferred, however, since diagnosis in the neonatal period is difficult and inexact. Furthermore, total correction will require an open heart procedure in most or all of these patients and this technique is at present unsatisfactory in the newborn. The cardiac lesions noted in the reported patients were not so severe as to require immediate correction. A possible exception to this generalization is the repair of ventricular diverticula which may be amenable to immediate correction.

Some of the sternal defects will not require correction. Minor abnormalities of the lower sternum are not cosmetically or physiologically serious. Should there be an extensive defect, however, immediate repair must be strongly considered since the correction of large defects becomes progressively more difficult with advancing age.

In those cases in which an omphalocele is present, immediate surgical intervention is, of course, mandatory and it would seem logical to attack any other reparable defects at that time. Certainly in such cases there can be no justification for deferring repair of the diaphragmatic defect. Should the omphalocele be sufficiently large so that primary repair is difficult or impossible, necessitating simple closure of the skin over the viscera, it would seem doubly important to close the diaphragmatic defect to avoid

the exertion of undue pressure on the intrathoracic contents and herniation of abdominal viscera through this defect into the pericardium. Repair of even the largest diaphragmatic defects of the type seen in these patients can be accomplished in the newborn (as in our Case 1) by bringing the remaining diaphragm anteriorly and attaching it to the anterior thoracic wall and costal margin. This is easily done since the remaining diaphragm is structurally normal and permits the necessary anterior displacement without undue tension. This maneuver simultaneously obliterates the pericardial defect.

Should the patient have an intact skin covering over the defect in the muscular portion of the abdominal wall, repair might be deferred. There is little to be gained by such delay, however, since the ability of the newborn to withstand operation is well known and will not be significantly augmented until well past the neonatal period. It is generally conceded that most congenital defects do not become more amenable to repair with increasing age but rather that correction becomes more difficult.

The technique of abdominal wall closure in such patients is worthy of specific comment. The lateral displacement of the rectus muscles precludes their approximation. In our Case 1, it was possible to develop a fascial structure which extended ventrally from the medial border of the rectus muscles and resembled linea alba. A strong closure of the abdominal wall defect was thus obtained using this local tissue. Linear relaxing incisions in the anterior rectus sheath are important in relieving tension on this closure.

TABLE III.—ANALYSIS OF CONGENITAL CARDIAC LESIONS IN 15 ADEQUATELY DESCRIBED PATIENTS

	No. of cases
Interventricular septal defect	15
Interatrial septal defect	8
Pulmonary stenosis	5
Tetralogy of Fallot	3
Left ventricular diverticulum	3
Patent ductus arteriosus	3
Anomalous venous return (caval)	3
Tricuspid atresia	1
Truncus arteriosus	1
Anomalous venous return (pulmonary)	1

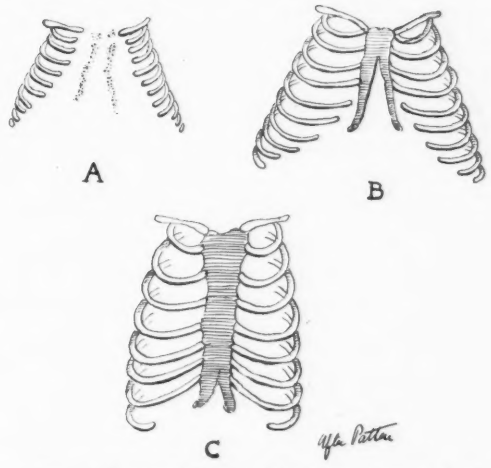

FIG. 15. The development of the human sternum showing progressive fusion of the lateral anlagen beginning at the cephalic end.

The increasing difficulty of repair attendant upon delay in correction is illustrated by Case 2. This patient was operated upon at 20 years of age, at which time it was impossible to isolate the fascial structure described in Case 1 and closure of the abdominal wall was accomplished only with difficulty by swinging flaps of anterior rectus sheath medially and the insertion of autogenous fascia lata as reinforcement. Extensive dissection of the pericardium from the heart and surrounding structures was necessary to accomplish the repair. Closure of the diaphragmatic defect was not considered feasible. In all probability, a much simpler procedure would have been possible in infancy.

SUMMARY

The consistent association of a group of congenital anomalies involving the abdominal wall, lower sternum, ventral diaphragm, pericardium, and heart has been studied in 21 patients, 5 of whom are herein reported. This complex should be considered as a specific syndrome. It is inadequate and inaccurate to consider such patients as examples of ectopia cordis.

The entire group of anomalies would appear to be closely related in embryologic development, arising as the result of defective formation and differentiation of the ventral mesoderm at about 14 to 18 days of embryonic life.

The unusual ventral defect of the diaphragm seen in these patients results from failure of the transverse septum to develop. This specific anomaly has failed to gain proper recognition in the classification of congenital diaphragmatic defects. Case 1 is the first recorded instance in which repair of this defect has been accomplished.

The consistent association of congenital intracardiac lesions has not been previously noted. An interventricular septal defect would appear to be invariably present.

The coexistence of serious unrelated anomalies appears to be rare.

Treatment should consist of immediate surgical repair except for the intracardiac abnormalities. Correction of the latter is probably better deferred until more exact diagnosis and safer surgical intervention are possible.

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STUDIES ON THE MECHANISM OF DEATH IN PULMONARY MICROEMBOLISM

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CONSIDERABLE EXPERIMENTATION since 1920 has not resolved the debate as to whether the mechanism of death in pulmonary microembolism is due to simple vascular obstruction or to a secondary reflex vasoconstriction. It is noteworthy that standard textbooks generally accept the concept of reflex vasoconstriction, whereas the consensus among investigators who have studied the problem is weighted toward the concept of simple vascular obstruction.

That massive pulmonary microembolization will result in death from mechanical vascular obstruction is an unchallenged fact. The concept that death may result from a lesser embolization plus an additive pulmonary reflex vasoconstriction is based upon two types of evidence. The earlier of these was based upon the observation that embolization of one lobe of the lung in dogs could produce pulmonary hypertension and death. Since ligation of the vascular supply to a single lobe is without effect, it was assumed that death in the embolized animals was due to vasoconstriction in the remainder of the pulmonary vascular bed. Subsequent investigations invalidated this assumption, however, by demonstrating that this "localized embolization" was, in truth, diffuse pulmonary embolization by virtue of retrograde passage of the particulate matter. When retrograde passage was prevented by tying the infusing cannula into the lobar artery, neither death nor pulmonary hypertension ensued. Not discounted, however, is the more recent evidence derived from canine heart-lung-head preparations which seems to support the theory of reflex vasoconstriction in pulmonary microembolism. Pretreatment with ganglionic blocking agents or total denervation of these preparations was found to exert a protective effect by considerably delaying the appearance of pulmonary hypertension and subsequent death in pulmonary microembolization.

The present study was undertaken to determine whether the protective effect of hexamethonium on the embolized heart-lung-head animal could be extended to the intact animal and, if so, whether simple vascular obstruction or reflex vasoconstriction could be identified as causative.

METHODS

Thirty mongrel dogs were used in the study. Sodium pentobarbital (30 mgm./kgm.) was administered intravenously for anesthesia, and the animals were heparinized. An endotracheal tube was inserted and, upon opening the chest, the lungs were inflated and respiration cycled with a positive pressure air respirator. A No. 18 polyethylene catheter was tied into a femoral vein for administration of pharmacologic agents; a very slow, continuous drip of isotonic sodium chloride solution was maintained to preserve patency. A No. F16 soft plastic catheter was tied into the right external jugular vein and placed so that the tip was just cephalad to the right atrium. A glass cannula was tied into a femoral artery and connected to a direct-writing mercury manometer. The chest was then opened through a left thoracotomy incision, and a pulmonary lobar artery was identified and ligated. A No. 20 polyethylene catheter was inserted into this artery proximal to the ligature and

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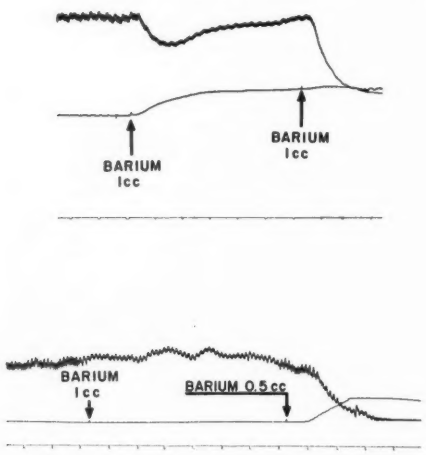

FIG. 1. Two experiments in group A. In each, the top tracing is femoral artery pressure, the middle is pulmonary artery pressure, and the bottom is the timer tracing. Tracings are cut off at the time of death.

threaded into the pulmonary artery. This catheter was connected to a second direct-writing mercury manometer.

A pilot study on 8 of the animals compared pressures obtained from the right atrium or superior vena cava with those from the pulmonary artery. In all of these dogs, the atrial pressures lagged markedly in reflecting pulmonary arterial pressure. Furthermore, these pressures decreased when pulmonary arterial pressures remained elevated. Therefore, in the experiments to be reported, only pulmonary arterial pressure was recorded.

Twenty-two dogs were used in the actual study and were divided into four groups to be discussed:

TABLE I.—AVERAGE SIZE (100 MEASUREMENTS IN EACH SPECIMEN) OF VESSELS EMBOLIZED WHEN BARIUM WAS INJECTED IN REPETITIVE DOSES UNTIL DEATH

Dog No.	*Time of biopsy*	*Average size* of embolized vessels, mm.*
2	Animal moribund	2.36
3-a	At 1st rise in P.P.	2.33
4	Animal moribund	2.23
5-b	At 1st rise in P.P.	2.34
8-a	At 1st rise in P.P.	2.32
12-a	At 1st rise in P.P.	2.28
Average		2.30

*In mm. of 440 × enlarged object.

Group A. Five animals were subjected to multiple injections of a 1:2 barium sulfate suspension into the jugular catheter until their death. Femoral and pulmonary artery pressures were continuously recorded on a kymograph. A biopsy specimen was taken from the left lung preterminally for histologic examination.

Group B. In 2 animals a No. 20 polyethylene catheter was inserted distally into the ligated lobar artery and tied in position. The lobe was then massively embolized through this catheter with the 1:2 suspension of barium sulfate. Continuous pressures were recorded from the femoral and pulmonary arteries. Tissue was taken from unembolized lobes to assure that there was no retrograde dissemination.

Group C. Ten animals were embolized with repeated, small amounts of the 1:2 barium sulfate suspension until the initial rise in pulmonary arterial pressure appeared. Five of these animals were then given hexamethonium via the femoral vein catheter until the maximal peripheral blood pressure effect was obtained. The remaining 5 animals were similarly treated with priscoline. After varying intervals (up to 8 minutes) following the injection of these agents, embolizations were again made repeatedly until death of the animal. Femoral and pulmonary artery pressures were recorded continuously. Biopsy specimens of the left lung were secured following exhibition of the drugs and further barium embolizations.

Group D. Five animals were given 100 milligrams of hexamethonium intravenously 8 minutes prior to barium embolization. Embolizations were repeated until death ensued. Femoral and pulmonary artery pressures were continuously recorded. Biopsy specimens of the left lung were taken at the first slight rise in pulmonary arterial pressure.

All of the biopsy specimens were fixed in formalin and stained with hematoxylin-eosin, Verhoeff-van Gieson, and Wilder's reticulum stain. The diameters of 100 consecutively observed vessels filled with

packed barium particles were measured in each of these specimens by an ocular microcaliper. Measurements were made in millimeters of the images magnified 440 times.

RESULTS

Exactly similar responses were forthcoming in each of the 5 dogs in group A which were subjected to multiple injections of barium until their deaths. The recordings of 2 of these animals are reproduced as Figure 1. If the initial barium injections were small in amount (0.25 to 0.5 ml. of 1:2 barium sulfate suspension), no pulmonary hypertension resulted. A point was then reached following which each barium injection produced a step-wise rise in pulmonary arterial pressure. Ultimately the peripheral arterial pressure precipitously dropped and the animal expired. The total amount of barium necessary to produce death in these animals ranged from 1 to 2 grams (2 to 4 ml. of suspension), the amount in each case roughly correlating with the size of the animal. Histologic examination of the lungs revealed the barium to be primarily obstructing the arterioles (Fig. 2). The average diameter of the embolized vessels was 2.3 millimeters of the image enlarged by 440 (Table I). There is seen to be little deviation from the mean.

The responses of the 2 animals to local embolization of one lobe were identical. The recording in 1 of these animals is reproduced as Figure 3. Pressure in the pulmonary artery did not change despite massive embolization. Histologic examination of tissue from the unembolized lobes revealed no scattered barium.

The 10 animals of group C, which were embolized repetitively until death and given hexamethonium or priscoline after the first rise in pulmonary pressure, succumbed in the same fashion and to the same amounts of barium (1 to 2 gms.) as did the animals in group A which were not treated with these drugs. No significant alteration in pulmonary pressure was noted in any of these dogs after the exhibition of relatively large doses of the drugs. Representative experiments are shown in Figures 4 and 5. It can be noted in Table II that there is no significant difference between the average diameter of the vessels embolized in these animals and those embolized in the animals of group A to which the drugs were not administered. Histologic examination revealed that the arterioles were predominantly involved.

FIG. 2. Barium embolus plugging a pulmonary arteriole. ×225.

A representative example of the consistent response of the 5 animals of group D which were subjected to pre-embolic treatment with 100 milligrams of hexamethonium is shown in Figure 6. A slight drop in pulmonary pressure appeared immediately following the injection of hexamethonium. This lasted for only a few seconds after which the pulmonary pressure returned to normal levels. Thereafter, repetitive barium embolizations failed to produce a rise in pulmonary pressure until a total amount of

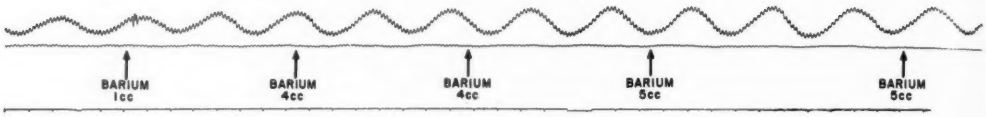

FIG. 3.

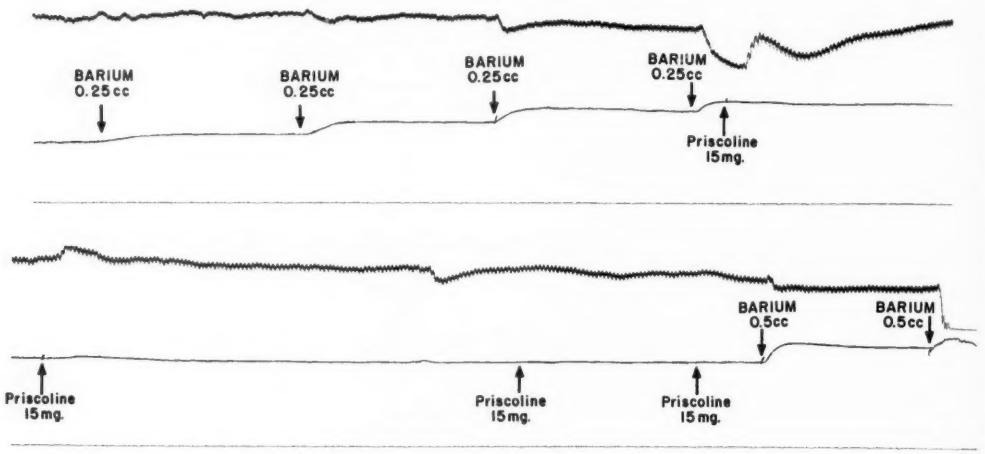

FIG. 4.

FIG. 3. Massive, repetitive barium embolization to one lobe. Upper tracing is from femoral artery; respiratory waves are prominent. Lower tracing is from pulmonary artery.

FIG. 4. A single experiment (bottom set of tracings is a continuation of the top set) in which priscoline was given after initial embolization and rise in pulmonary pressure.

barium had been given far in excess of those amounts lethal to animals in groups A and C. Ultimately, the terminal response to continued injections of barium is the same as the response in untreated animals. The amount of barium necessary to produce death in the dogs of this group was 6 to 10 grams as contrasted to the 1 to 2 grams in groups A and C. The average diameter of the embolized vessels in the lungs of these animals was 1.5 millimeters of the image magnified by 440 (Table III). Histologically, the predominantly involved vessel was seen to be the capillary (Fig. 7).

DISCUSSION

In 1920, Dunn embolized the lungs of various animals by intravenous injection of starch and oil particles. With large doses he noted a rapidly increasing venous pressure, systemic shock, and death, whereas with sublethal doses he noted only a transient rise in venous pressure without accompanying effect on peripheral arterial pressure. He concluded that these emboli were blocking pulmonary blood flow at the arteriolar level, and that there was compensatory vasodilation in the unobstructed portion of the arteriolar bed accounting for the transient nature of the pressure changes with sublethal doses. In 1928 Sternberg and Tamari, investigating the possible existence of vasoconstrictor tonus in the pulmonary arteriolar bed, injected India ink suspension into the veins of anesthetized, unanesthetized, and decerebrate rabbits. A much smaller amount of the suspension was required to kill the unanesthetized animals than the anesthetized or decerebrate animals. Furthermore, in the former group the particles were found predominantly in the arterioles whereas, in the latter two groups, they were found predominantly in the capillary bed. While these findings did not establish the

fact of vasospasm in pulmonary microembolism, they at least certainly suggested the existence of vasoconstrictor tonus in the pulmonary arteriolar bed. In 1935, Villaret and associates caused death by the intravenous injection of fine pumice. When vagus section preceded the pumice embolization, 7 times the embolizing dose had to be given before death ensued. With this indirect evidence, they postulated the evocation of a reflex vasoconstriction by sublethal microembolism which was abolished by vagus section.

In 1948, Smith and Hara failed to produce death when relatively large particles were injected into a lobar artery. When, however, they injected a suspension of starch, there occurred a sharp rise in pulmonary arterial pressure, shock, and death. They postulated a reflex vasospasm in the unembolized lobes originating from receptors in the vasculature of the embolized lobe. In 1951, Daley and his associates reproduced the experiment of Smith and Hara using microemboli. Upon examining the "unembolized" lobes histologically, they found that these lobes also had been embolized. This obviously occurred by retrograde dissemination of particles since, when they tied the cannula into the lobar artery before embolizing, they could not kill the animals by this means and the untreated lobes were now found to be free of particulate matter. In 1953, Cate and associates repeated the same observation by using catheters with inflatable balloon tips. It is evident, from these observations, that Smith and Hara were producing a diffuse mechanical block in the pulmonary vascular bed and that, therefore, no premise for postulation of reflex vasoconstriction existed.

Although the observations of Villaret and associates and others remained unexplained, these latter demonstrations molded general opinion against the existence of a vasospastic component in pulmonary microembolism. Further evidence against the existence of vasospasm following pulmonary microembolism was offered by Knisely and

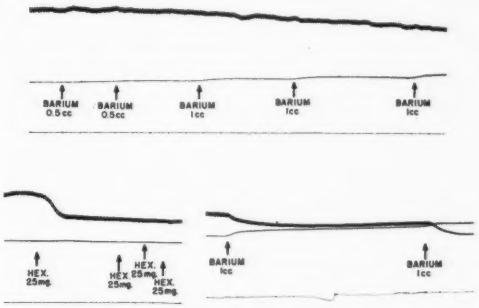

FIG. 5. A single experiment (bottom set of tracings is a continuation of the top set) in which hexamethonium was given after initial embolization and rise in pulmonary pressure.

his associates who studied the lungs of animals in vivo by direct microscopy during microembolization. They noted that the unembolized vessels remained either the same or increased in size. They, therefore, concluded that there is no vasospastic component in the vascular response to pulmonary microembolism.

The theory of a vasospastic component was revived in 1955 by Price, Hata, and Smith who embolized canine heart-lung-head preparations with 1:1 suspensions of

TABLE II.—AVERAGE SIZE (100 MEASUREMENTS IN EACH SPECIMEN) OF VESSELS EMBOLIZED WHEN BARIUM WAS INJECTED PRIOR TO, AND FOLLOWING, ADMINISTRATION OF HEXAMETHONIUM OR PRISCOLINE

Dog No.	*Average size* of embolized vessels, mm.*
3-b	2.06
5-c	2.16
8-b	2.00
12-b	2.18
Average	2.10

*In mm. of 440 × enlarged object.

TABLE III.—AVERAGE SIZE (100 MEASUREMENTS IN EACH SPECIMEN) OF VESSELS EMBOLIZED WHEN ANIMALS WERE PRETREATED WITH HEXAMETHONIUM

Dog No.	*Average size* of embolized vessels, mm.*
1	1.66
9	1.40
10	1.55
11	1.34
Average	1.49

*In mm. of 440 × enlarged object.

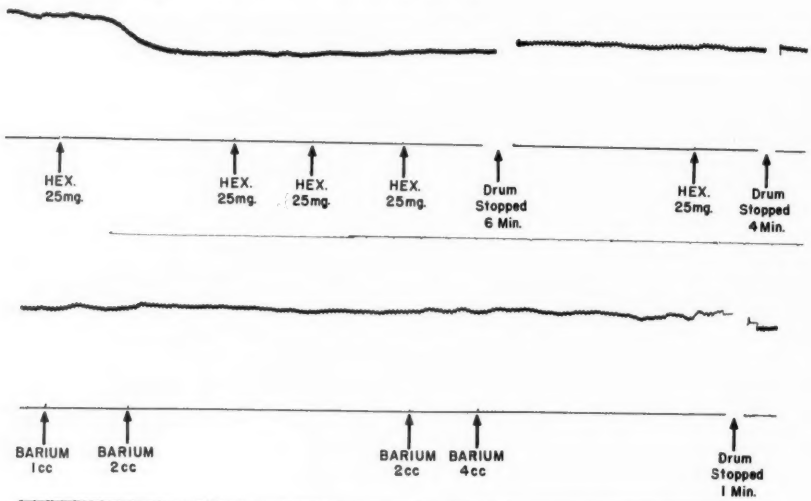

FIG. 6. A representative experiment in group D, showing effects of hexamethonium administration prior to embolization.

barium. They observed the usual abrupt pulmonary hypertension, a fall in cardiac inflow, peripheral arterial hypotension, and death. These responses were significantly retarded by pretreatment with hexamethonium or with surgical sympathectomy. Also, the response could be reversed if, at its height, the preparation was converted to a Starling heart-lung preparation by sudden decerebration. From these findings, they postulated that miliary embolization produces a pulmonary vasoconstriction which can be prevented by sympathectomy or hexamethonium pretreatment and can be reversed by conversion of a heart-lung-head to a heart-lung preparation.

Out of all of this inquiry, the observations which remain valid are those which demonstrate a delayed appearance of pulmonary hypertension and death, and which arise out of common experimental conditions which are such as are known normally to depress arteriolar vascular tone. This fact does not directly implicate vasospasm in the mechanism of death in pulmonary microembolism. Theoretically, however, the explanation of this fact might lie in the phenomenon observed by Sternberg and Tamari, namely, when arteriolar tone is reduced the ensuing dilatation might allow particulate matter, which would otherwise block the arteriolar bed, to pass into the capillary bed. In the latter situation, a much greater amount of material would be required to obstruct the vascular bed critically than in the former.

In the present study, the effects of pulmonary microembolism were re-examined

in the intact animal and the site of their lodging in the pulmonary vascular bed was ascertained. Specifically studied were the pulmonary vascular responses to: (1) localized lobar emboli; (2) diffuse pulmonary emboli; (3) diffuse pulmonary emboli in animals pretreated with hexamethonium; and (4) diffuse pulmonary emboli with administration of hexamethonium or priscoline following the initial, persistent rise in pulmonary arterial pressure.

The lack of pulmonary vascular response to localized embolization is an observation previously made by others. Repeated, diffuse embolization led to a step-wise rise in pulmonary pressure until suddenly there appeared a precipitous fall in peripheral arterial pressure and death. The emboli were found predominantly in the arterioles. The same responses were yielded by the animals to which a ganglionic blocking agent was administered after the first effects of embolization were obtained, and the emboli were again found predominantly in the arterioles. When the animals were pretreated with hexamethonium, a relatively great resistance to embolization was observed. In this situation, the emboli were found to be located predominantly in the capillaries.

The protective influence of hexamethonium pretreatment seems to result from arteriolar relaxation which allows the particulate matter to pass into the capillary bed. When the emboli collect in the capillary rather than the arteriolar bed, much greater quantities are necessary to produce the same degree of mechanical obstruction since the former possesses some 600 times the capacity of the latter. It is neither necessary nor logical to invoke the concept of vasospasm to explain the findings of this study. The differences in response result from the level of occlusion in the vascular bed.

That the ratio of the size of the embolized arteriole to the size of the embolized capillary is not the same as the ratio of these two structures in their normal state seems to be the result of capillary distention caused by the embolic material.

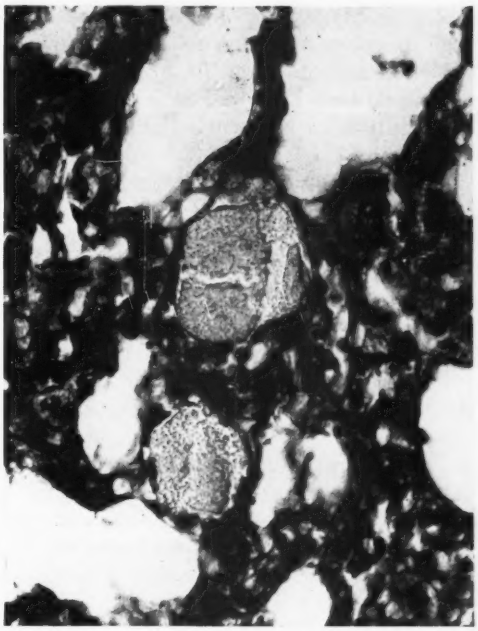

FIG. 7. Barium emboli plugging pulmonary capillaries. ×560.

That hexamethonium has no effect on the response to microembolization once pulmonary hypertension obtains, whereas the conversion of a heart-head-lung to a heart-lung preparation reportedly does, cannot be explained by the present study. Perhaps with the latter stimulus the embolized arteriolar bed is sufficiently dilated so that the particulate matter passes on into the capillary bed, while in the former condition the stimulus is not sufficient to provoke this alteration. This concept should be studied further.

SUMMARY

1. Diffuse pulmonary microembolization with barium in the intact, lightly anesthetized dog results in prompt pulmonary hypertension, peripheral arterial hypotension, and death. Embolism is primarily to the arteriolar bed.

2. Hexamethonium and priscoline do not alter this response when exhibited following sublethal embolization. Embolism is to the arteriolar bed both before and after administration of these ganglionic blocking agents.

3. When the animal is pretreated with hexamethonium, a marked degree of protection against pulmonary microembolization is conferred. Embolism in this situation is to the capillary bed.

4. There was no evidence of a vasospastic phenomenon in these studies. The various vascular responses described correlated with the size of the pulmonary vessels that were mechanically blocked.

5. It is postulated that this phenomenon is the true basis of those previous observations which were thought to establish the existence of vasospasm in pulmonary microembolization.

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FIVE YEAR OBSERVATIONS ON UNSUPPORTED FRESH VENOUS GRAFTS OF THE AORTA IN DOGS

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THERE HAVE BEEN a number of experimental investigations of autogenous veins as arterial substitutes, but most of these have dealt with relatively short term observations. The longest period of study is that of Nabatof and associates who described the changes in 2 abdominal aortic vena cava implants after 3 and 4 years. Their report is of only 2 animals, however, and does not provide a very broad basis for judgment of such grafts. Obviously, the expense of long term maintenance of animals ($915.00 for board and food alone for each dog in our series) precludes the use of large groups.

This report is presented to describe the physical and functional characteristics of 4 autogenous vein grafts implanted in the aortas of dogs for more than 5 years.

The clinical use of autogenous venous grafts to replace diseased and excised segments of large arteries and the aorta has been rather limited, and properly so. Although such grafts have been shown to be useful in substituting for short segments of small diameter peripheral vessels, such as the femoral, popliteal, and brachial arteries, most surgeons have shunned their application to the aorta and its primary branches. Most experimental investigations of the use of vein grafts in arterial replacement of large vessels have shown that the implanted segment becomes dilated within a period of a few weeks, and that within a few months aneurysmal dilatation is the rule, with frequent rupture.

Except for the certainty of such dilatation, autogenous vein would seem to provide a nearly ideal source of arterial grafting material. Functionally, they have been found to be superior to arterial homografts in terms of degeneration. Accumulating evidence dictates that homologous and heterologous vascular tissues are subject to a high incidence of degenerative change with consequent thrombosis when used as vascular replacements. Immuno-chemical efforts to modify the protein structures of arteries are based on the hope that a lessening of host response to the chemically foreign implant will lead to a better anatomic and functional result in grafting. Such efforts together with the search for an ideal plastic substance from which to fabricate prostheses for vascular replacement have stimulated what has probably been the most intensive and exhaustive investigation of a single problem in the history of surgery, if one will accept the witness of the surgical literature since 1945.

METHOD

All the experiments reported here were begun as a part of a larger investigation of several aspects of vascular replacement. One facet dealt with the differences between fresh homologous and fresh autogenous venous grafts. From each of these groups representative dogs were set aside for long term observation. Included were: autogenous external jugular vein to abdominal

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FIG. 1. The final aortographic appearance of each of the 4 venous aortic grafts. Dog B (C-26) is the only homograft in the group; the others are all venous autografts. (See the text for details.) There is complete patency and function of all grafts after 5 years' implantation. The graft from dog C (Big Boy) is the only one of the group which has undergone any significant aneurysmal dilatation.

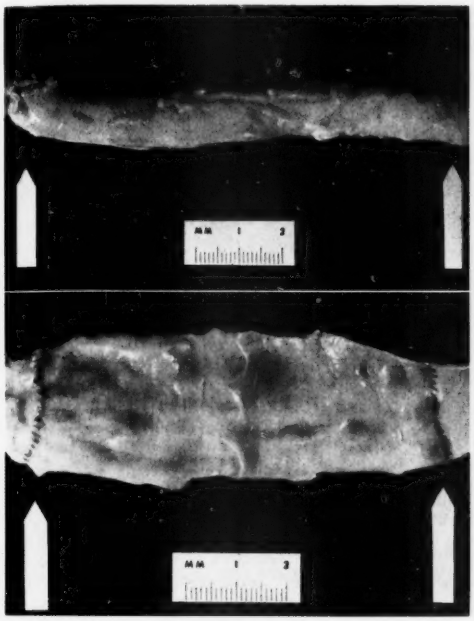

FIG. 2. The inflated (100 to 120 mm. Hg) and internal appearances of the venous autograft from dog A (C-42). Anastomoses are indicated by arrows. Note the tricusp venous valve, which was reversed at implantation.

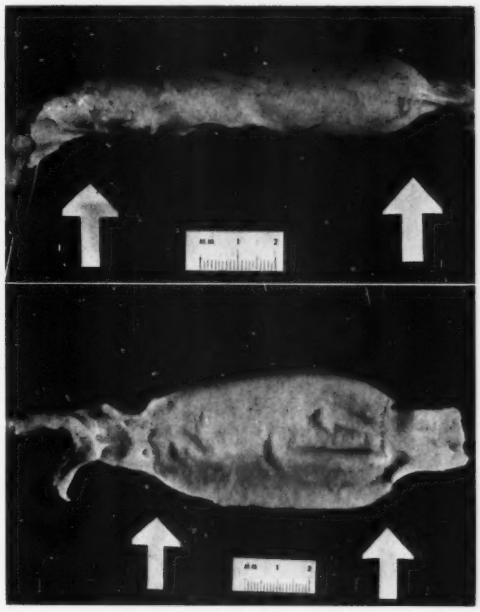

FIG. 3. Inflated and internal views of the single venous homograft from dog B (C-26) in this series. Arrows indicate anastomoses. Note the thin wall and smooth intimal surface of the grafted segment.

aorta (1 dog); inferior vena cava autograft to abdominal aorta (2 dogs), and inferior vena cava homograft to abdominal aorta (1 dog).

The initial surgical grafting procedures were all carried out under aseptic operating room conditions. Donor venous segments—whether autogenous or homologous—were also obtained under sterile conditions at the time of operation. All anastomoses were made with a continuous over-and-over suture, using No. 4-0 or 5-0 atraumatic vascular silk sutures.

After full recovery from operation the dogs were maintained at a farm where unrestricted activity was allowed, and where as healthful an over-all existence as possible obtained. The dogs were recalled at intervals for a general check. All grafts were evaluated for dilatation by periodic aortography at intervals of several months to a year. For this procedure the dogs were lightly anesthetized with nembutal, and contrast medium (diodrast or urokon) was injected through a catheter passed into the aorta through either a brachial or femoral artery. Only 1 of the animals was sacrificed sooner than 5 years after grafting.

RESULTS

Immediate functional result. All animals recovered promptly from the initial procedure and had uncomplicated postoperative courses with normal peripheral arterial pulses. There was no instance of paraplegia or other untoward sequel to suggest early thrombosis or overlong operative cross-clamping of the aorta.

Intermediate result. The dogs continued well and healthy throughout the first 2 years of the study. Aortography was carried out as described, and by the end of the fourth year, marked dilatation was noted in only 1 graft. This dog ("Big Boy") was

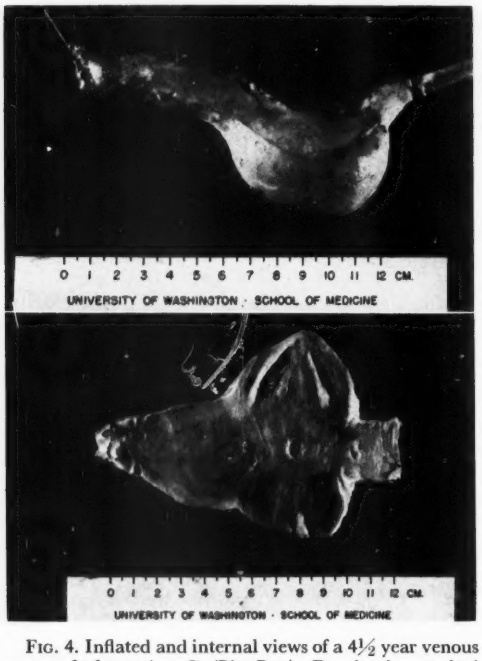
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FIG. 4. Inflated and internal views of a 4½ year venous autograft from dog C (Big Boy). Despite its marked aneurysmal dilatation, this graft functioned perfectly and has a smooth intima (see Fig. 6).

1 of the 2 with inferior vena cava autografts. The aneurysm formation did not enlarge or change significantly during the subsequent year, however.

Late result. The 4 dogs which are the subject of this report were sacrificed 5 years after implantation of the grafts, with 1 exception. Dog C (Big Boy) was noted about 4½ years after operation to have an enlarged abdomen, edema of the feet and legs, and hindquarter weakness. The dog's age was then about 12 years, and because of the progressing incapacity it was sacrificed for humane reasons. The total duration of the vena cava-aorta graft was thus somewhat shorter than the others, but approaching 5 years (Table I).

TABLE I.—TYPE AND DURATION OF 5 YEAR VENOUS GRAFTS OF THE AORTA IN DOGS

Dog	*Graft*	*Duration*
A (C-42)	Autograft from external jugular vein	5 years, 1½ mos.
B (C-26)	Homograft from inferior vena cava	5 years, 1 mo.
C (Big Boy)	Autograft from inferior vena cava	4 years, 9 mos.
D (A-49)	Autograft from external jugular vein	5 years, 1 mo.

At the time of sacrifice, a final aortogram was done in each of the animals. The abdomen was opened, the grafts extirpated along with the entire abdominal aorta and iliac arteries. Each graft was carefully inspected, palpated, and measured. Before being opened, each was inflated to 120 millimeters of mercury air pressure, and its external surface photographed. Inspection of the grafts' intimal surfaces and removal of portions for microscopic section completed the study. The findings in the 4 grafts will be considered under several headings.

X-ray appearance. As previously mentioned, aortography was performed at intervals of several months to a year in each of the grafted animals. Thus, a series of roentgenograms is available for each animal and examination and interpretation of these films constitute an important part of this study. Space does not allow reproduction of all of the x-ray pictures taken. In Figure 1 are shown the final aortograms made before sacrifice of each of the 4 dogs. The aortogram labeled "Dog B (C-26)" is the only venous homograft in the group, all others being venous autografts.

The most striking thing to be noted from inspection of the 4 aortograms is that there is complete patency of each. None of the grafts became occluded, a result which is rather to be expected of technically well done aortic grafting. Second, it is to be noted that there is dilatation of varying degree of all the grafts. The most spectacular change is that which has taken place in the graft in dog C. This graft was taken from the inferior vena cava and immediately implanted as a fresh autograft so that neither preservation nor age of the graft can be incriminated as causative of the marked dilatation. (This is the animal which was sacrificed a few months before the end of the contemplated 5 year obser-

vation period. At autopsy, this dog was found to have advanced cirrhosis of the liver and ascites.) The proximal aneurysmal dilatation is atypical of the group as a whole, but had in no way impaired the distal circulation.

The external jugular venous autograft in dog A (C-42) was in place slightly over 5 years (Table I). The graft has a slightly greater diameter throughout than that of the host aorta, and there has been an increase in length with a resultant mild sigmoid tortuosity. There is certainly no luminal narrowing or interference with filling of the vessels of the aortic trifurcation. When compared with aortograms taken 1 and 2 years before, little change can be seen in the interval.

Dog B (C-26) is the only animal in the group having a venous homograft. This graft was in place 1 day longer than that of dog A. The fusiform dilatation of the entire graft is quite striking, particularly in its proximal one-third where the aorta-graft diameter ratio is 1 to 2.2. At the distal anastomosis there is rather obvious constriction of the lumen. These observations are of interest and will be specifically considered in a later section.

The fourth member of the group, dog D (A-49), has the most normal final aortographic appearance of all. There is only a very slight increase in internal diameter of the graft, and no increase in length. Morphologically, this was the best end result of the group and was in place as long as the others (Table I).

Gross appearance. After completion of the final aortographic studies, all animals were sacrificed and their grafts excised in continuity with proximal and distal segments of the host aorta for photographic purposes. So that comparisons could be made with the aortograms of each, the grafts were inflated with air at a pressure of 100 to 120 millimeters of mercury. Figures 2 to 5 show the inflated and open views of each of the 4 grafts. (The negative of the inflated view of the graft from dog D (A-49) was inadvertently destroyed and, therefore, is not shown.)

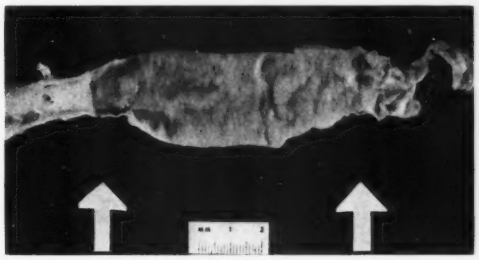

FIG. 5. Internal appearance of the 5 year venous autograft from dog D (A-49). The inflated view was lost through error. Reference to Figure 1 will confirm the impression that this graft retained near-normal proportions and functioned perfectly.

In general, gross examination of the excised grafts confirms the impressions from aortography. The graft from dog A (C-42) is of quite uniform diameter throughout, is pliable and without atheromatous degeneration. The intimal surface is smooth and shiny with no irregularities. A tricusp valve (reversed) is preserved, with the cusps firmly adherent to the vessel wall.

The venous homograft from dog B (C-26) (Fig. 3) also showed a complete lack of adverse change in either its wall or intimal surface. It, too, is soft and pliable, but inelastic.

Grafts in dogs C and D (Figs. 4 and 5) again show dilatation. The bizarre saccular aneurysmal dilatation of graft in dog C was found to originate exactly at the proximal anastomosis to the aorta and did not involve the latter.

All 4 of the grafts have certain common features. The vein wall had become thickened, fibrous, and inelastic. The vessel no longer looks or feels like a vein, but more nearly resembles artery. This "arterialization" of a grafted vein has been noted by others. The lack of an internal elastic lamina and the constant maximal distention imposed by aortic pressure doubtless account for the changes noted.

It is also important to note the very minimal reaction about the grafts. While

there was adherence of the adjacent structures and connective tissue to the grafts, there was not the dense, fibrous impenetrable reaction so frequently found enmeshing arterial homografts. Curiously, the 1 homograft in the group, dog B (C-26), was grossly as free of such reaction as the 3 autografts. It would seem reasonable to think that the reaction about the graft would be in direct proportion to the total volume of tissue involved, i.e., an arterial homograft with its thickened wall and with a 3 or 4 times greater mass of tissue to be replaced by host cells would induce a proportionately greater fibrous response.

Microscopic appearance. Histologic study of the grafts and the host aorta was the final step in evaluation of the group. In Figure 6 are reproduced 3 photomicrographs of representative sections of 3 of the grafts. All are taken to include 1 anastomosis of vein to aorta, and all are oriented intima up, with the vein graft to the left-hand side of the arrow in the photograph. Grafts in dogs C and D show thickening of the graft to approximately the thickness of the aortic wall. The result in both is the formation of a fibrous, but cellular "media." In each of these autografts, the muscular layer of the vein graft is thin, but of essentially normal appearance, underlying the thickened, arterialized "media." There are, of course, no organized elastic structures in the vein wall. The appearance of the venous homograft (dog B) is distinctly different from that of the autografts. While it was not possible grossly to distinguish this graft from the others, due to its pliability and smooth intima, there are marked microscopic differences. First, there has been complete loss of the muscular layers of the graft, with replacement by dense fibrous tissue. The fibrous "media" and overlying intima have essentially the same appearance as those of the autografts, however. In all the grafts there has been a firm fibrous healing at the anastomoses without significant roughening or projection into the lumen.

DISCUSSION

Anatomically and functionally, the end result in this group of abdominal aortic venous grafts was excellent. There was no instance of thrombotic occlusion or luminal narrowing. Neither was there rupture of any graft. Two of the grafts, including the 1 homograft, underwent what must be called significant aneurysmal dilatation. In view of the complete lack of atheromatous degeneration in either of these latter grafts, it must be concluded that the dilatation was due entirely to the nature of the wall of the grafted vein itself. It should be noted that the graft which underwent the most striking and extensive dilatation was one of the autografts, whereas the venous homograft, while dilated to a luminal diameter of more than twice normal, is at least a better anatomic result.

Certainly, little can be said in generalities from study of so small a group of test grafts as this, but it would appear that the aortic restoration was in each instance acceptable for what was nearly the remaining life span for each animal. Further, the dilatation which occurred in 3 of the 4 grafts took place early in the postgrafting period, so that during the last 2 years of the duration of the grafts there was no noticeable change in diameter.

In the 3 grafts here reported in which significant dilatation occurred, the process began at the proximal anastomosis and involved the graft only, without dilatation of the host aorta. The resultant change is one of fusiform, tapering increase in diameter with a normal graft diameter at the distal anastomosis. The fundamental concepts of Emile Holman concerning poststenotic dilatation would seem to apply here in accounting for the inequality of increase in luminal diameter of the grafts (1, 2). Such a mechanism can accommodate even the instance of localized lateral aneurysmal dilatation of the graft shown in dog C (Fig. 1). This sort of dilatation and deformity may result from angulation or irregularity of the anastomosis so that the turbulent current and their

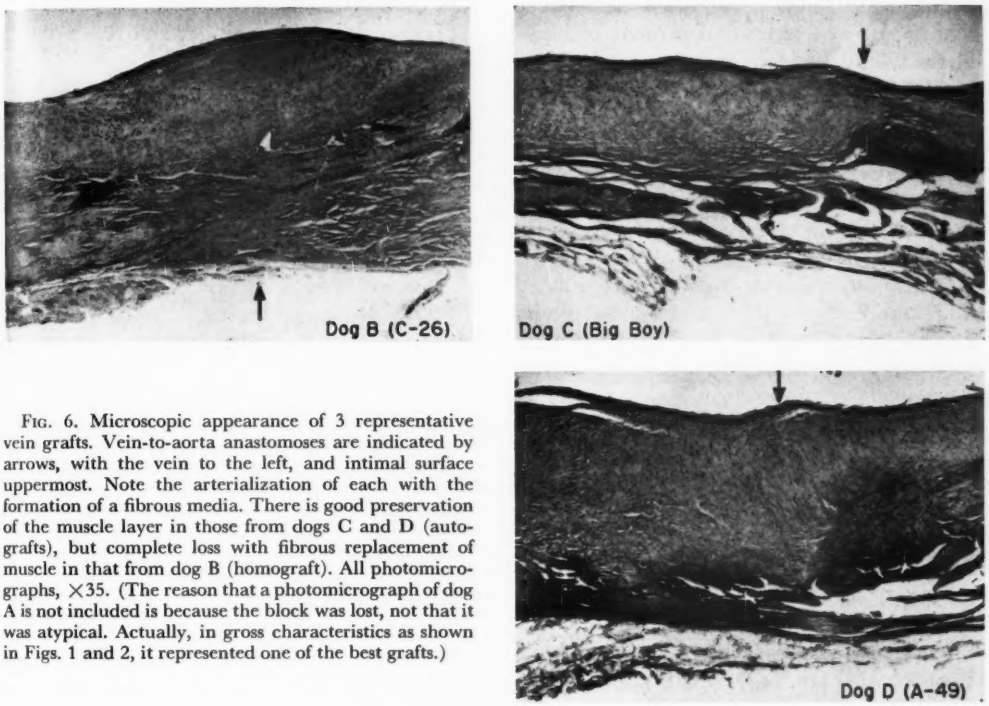

FIG. 6. Microscopic appearance of 3 representative vein grafts. Vein-to-aorta anastomoses are indicated by arrows, with the vein to the left, and intimal surface uppermost. Note the arterialization of each with the formation of a fibrous media. There is good preservation of the muscle layer in those from dogs C and D (autografts), but complete loss with fibrous replacement of muscle in that from dog B (homograft). All photomicrographs, ×35. (The reason that a photomicrograph of dog A is not included is because the block was lost, not that it was atypical. Actually, in gross characteristics as shown in Figs. 1 and 2, it represented one of the best grafts.)

lateral forces are exerted unequally against the graft wall.

The use of autogenous vein as a vascular replacement in human clinical practice has been so well characterized and accepted that further discussion here is pointless. We wonder, however, if some of the accepted limitations of the procedure cannot be modified, or at least opened to question. If some mammalian venous grafts of the aorta can survive for as long as 5 years, and undergo no more than moderate dilatation, it would seem that other venous grafts could be made to do so. In this small group, the most striking feature noted in all the grafts—including the 1 venous homograft in the series—was that there was no detectable atheromatous degeneration or significant loss of pliability. This is a rather unexpected result in the sense that many autogenous *arterial* aortic grafts will have undergone marked change during a similar period. A number of anatomic differences between vein and artery may contribute to the better late result with vein grafts. First, as already mentioned, a vein graft has a much thinner wall than an arterial segment, so that host invasion, phagocytosis, and replacement would be a much less vigorous and protracted process if the grafted venous segment were of homologous origin. When autogenous vein is used, it is easy to think that revascularization and complete survival of the full thickness of the thin graft wall could be accomplished more easily and regularly than of the thicker wall of an arterial segment. Second, and perhaps most important, is the fact that veins do not have an organized elastic layer. The internal elastic lamella of aortic and arterial segments has been abundantly incriminated in the pathogenesis of arteriosclerotic degeneration in grafts, and increasing evidence indicates that a similar chain of events may account for the same process as it occurs in normal aging. It would seem reasonable to

think, then, that a vein graft, with its scanty and scattered endowment of elastic fibers would have only a small propensity for localized degeneration and atheromatous plaque formation. In a thin-walled graft, dissolution and host absorption of scattered elastic fibers would be relatively easily accomplished before such fibers could become nidi for degeneration and eventual calcification.

Many investigators have dealt directly and indirectly with the physicochemical parameters of vascular grafting in attempts to modify the host-graft response. Certain methods of enzymatic treatment have been shown favorably to alter the host response to homologous arterial implants. It remains true, however, that such grafts are still chemical "foreign bodies." Autogenous venous grafts are free of this stigma, and if such grafts could be treated so as to make them less subject to pulsion dilatation they might serve better as aortic and arterial replacements than even autogenous artery. If such a process can be devised it will, with the easy availability of suitable autogenous venous material, greatly improve the technical course and functional outcome of many vascular restorative procedures.

Investigations in progress in our laboratories tend to indicate that chemical modification of vascular grafts holds considerable promise. It is to be hoped that the use of autogenous vein in arterial grafting will enjoy a rejuvenescence and expansion with a consequent improvement in over-all result.

SUMMARY

The aortographic, physical, and microscopic features of a group of 4 venous aortic grafts of 5 years' duration in dogs are presented.

The functional result in all the grafts was excellent, with no instance of occlusion or rupture.

Dilatation of varying degree occurred in 3 out of 4 of the grafts. In each instance, the dilatation occurred early in the 5 year period of observation and was not progressive.

The gross and microscopic appearance of the extirpated grafts confirmed the impression of excellent result, with good preservation of structure of the grafts, pliability, and lack of circumvascular reaction.

Certain very desirable features of the use of autogenous vein in aortic arterial restoration are discussed with reference to the chemical modification and potential extension of the uses of such grafts.

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CERVICOCOLPITIS (VAGINITIS) EMPHYSEMATOSA

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CERVICOCOLPITIS EMPHYSEMATOSA is an unusual but distinctive lesion which is characterized by the presence of small gas-filled spaces in the lamina propria of the vagina and frequently also beneath the squamous mucosa of the cervix uteri. The causal and formal genesis have defied a logical explanation and remain obscure. The first description of this entity is credited to Huguier in 1847. Winckel in 1871 reported 3 examples of the condition in pregnant women under the heading, colpohyperplasia cystica. The name "vaginitis emphysematosa," under which most cases are reported, was introduced by Zweifel in 1877. This term does not, however, indicate involvement of the uterine cervix which is frequent if not constant. For this reason Mackles and Gettinger employed the term colpocervicitis and we prefer the designation cervicocolpitis, which stresses the constant vaginal involvement but also embodies the less obvious and possibly less constant involvement of the uterine cervix.

Herman in 1891 reviewed the early medical literature, primarily German, on the subject and reported what he considered to be the first example in the English literature. Seventeen of 21 cases that Herman reviewed occurred in pregnant women. The first report in the American literature was by Jackson and Wright in 1898. Their 2 cases were nonpregnant women who had recently had supracervical hysterectomies. During the twentieth century, articles on the subject have been infrequent and confined largely to the recording of individual cases. Buckingham and McClure in 1954 found fewer than 20 case reports of this condition in the American and British literature. The lesion, however, would not appear to be as infrequent as this statement suggests because the 3 cases reported by Ingraham and Hall were apparently encountered in a period of 1 year.

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CLINICAL MATERIAL AND OBSERVATIONS

Eight examples of cervicocolpitis emphysematosa were found in the material of the Department of Pathology, University Hospital, University of Michigan, during a period of 17 years. Four cases were incidental discoveries at necropsy, there being no clinical indication of the condition. The other cases were diagnosed by biopsies of the vagina and uterine cervix which were done during the investigation of leucorrhea with the purpose of excluding a neoplasm. The ages of the patients ranged from 32 to 67 years with an average age of 49 years. All patients had been or were married and, with 1 exception, had had children. Four patients had passed the menopause by periods of 22, 15, and 13 years, and by 4 months. None of the other patients was pregnant at the time the diagnoses were made. One woman (Case 3) had an abortion approximately 3 months prior to her death when the necropsy revealed the unsuspected vaginal lesion.

Three of the 4 patients in whom the lesions were found at necropsy, died of cardiovascular disease with congestive cardiac failure. The death of the fourth woman was due to chronic progressive pulmonary emphysema and fibrosis with chronic cor pulmonale. Two patients had gynecologic examinations 2 weeks and 1 month prior to their deaths and no lesions were observed. One patient in whom the diagnosis was made by biopsy also had chronic rheumatic heart disease with congestive cardiac failure and a second had generalized arteriosclerosis with minimal congestive cardiac fail-

ure. The latter patient had received theelin intramuscularly before admission to the hospital. Another patient who developed the condition while in the hospital, prior to a fifth stage thoracoplasty, had been placed on synthetic estrogen therapy 1 month before the lesions were noted.

Three of the 4 patients in whom the disease was diagnosed by biopsy complained of a vaginal discharge. The fourth patient was investigated because of a difficulty in penetration during intercourse. Repeated examinations with biopsies were done on 2 patients.

RÉSUMÉ OF CASE REPORTS

CASE 1. The patient was a 58 year old obese Negro woman, para 1, gravida 1, who was admitted to the hospital with the complaints of swelling of the legs and persistent ulcers above the ankles. These signs were first noticed 5 months prior to admission. One year before admission a diagnosis of diabetes mellitus was made and the disease was controlled by diet and insulin. She was treated on 2 occasions during the past year for congestive cardiac failure. Menopause occurred at the age of 45 years and there had been no vaginal bleeding or discharge since then. The clinical diagnoses were atherosclerotic heart disease with congestive heart failure, chronic stasic ulcers of lower extremities with cellulitis, and controlled diabetes mellitus. Systemic antibiotic and local therapy were begun the evening of admission. The following morning the patient suddenly developed acute dyspnea and respirations ceased within a few minutes.

Necropsy, 2 hours after death, revealed advanced atherosclerosis with coronary arterial thrombi and old and recent myocardial infarcts. All viscera showed advanced passive congestion. There were ascites, bilateral pleural effusions, and marked pitting edema of the lower extremities. The uterus and ovaries were atrophic. The mucosa of the vaginal portion of the uterine cervix and of the vagina appeared intact and glistening but beneath it were numerous cystic spaces containing gas; the largest measured approximately 1 centimeter in diameter. No similar lesions involved the intestine or urinary bladder.

CASE 2. The patient was a 36 year old white woman, para 0, gravida 0, whose final admission to the hospital was on March 27, 1954. She had had rheumatic fever at the age of 15 years and had experienced exertional and nocturnal dyspnea for 10 years. Previous investigations led to the diagnosis of chronic rheumatic heart disease with mitral stenosis and atrial fibrillation. She had had 3 episodes of severe congestive cardiac failure. The final admission was for active chronic rheumatic heart disease with congestive cardiac failure and a possible urinary tract infection. The patient had no specific gynecologic complaints and menstrual periods had been regular. A pelvic examination 2 weeks prior to death revealed a smooth vaginal mucosa and no submucosal cystic lesions were observed.

The important pathologic diagnoses were: active chronic rheumatic pancarditis with mitral, aortic, and tricuspid valvular stenosis; mural thrombus in left atrium; cardiomegaly; chronic passive congestion of viscera; anasarca; and subcutaneous rheumatic nodules. The uterus measured 7.5 by 5 by 2.5 centimeters and there were no significant corporal lesions. Both ovaries contained multiple atretic follicular cysts. The fallopian tubes were absent. The mucosa of the vagina was markedly irregular with elevated gray-white plaques. When sectioned, smooth-walled cystic spaces which contained gas were visible beneath the mucosa of the vagina and the vaginal portion of the uterine cervix.

CASE 3. The patient was a 32 year old white woman, para 8, gravida 9, who was admitted to the hospital on June 22 and died on July 27, 1948. Her last normal menstrual period was on February 18, 1948. An abortion in April was followed by an acute septic endometritis and acute pelvic inflammation. Treatment was intermittent prior to admission and consisted of unknown amounts of sulfonamides, streptomycin, and penicillin.

On admission to the hospital the blood pressure was 94/50 millimeters of mercury; pulse, 150 per minute; respirations, 25 per minute; temperature, 100 degrees F.; and white blood cell count, 12,600 cells per cubic centimeter. A blood culture yielded a heavy growth of Staphylococcus aureus and cultures which were made throughout the course of the disease remained positive in spite of heavy and varied antibiotic therapy. The clinical diagnosis was acute bacterial endocarditis.

A gynecologic examination shortly after admission revealed normal external genitalia, smooth vaginal mucosa, soft uterine cervix, no significant enlargement of the uterus, and no adnexal masses, although the areas were quite tender. No cystic areas were described in or beneath the mucosa of the vagina or uterine cervix. The gynecologic diagnosis was postabortal pelvic inflammation.

The significant final pathologic diagnoses were: acute staphylococcal endocarditis of the tricuspid valve, multiple pulmonary abscesses with gangrene, right hydrothorax, peripheral edema, ascites, hepatic necrosis, septic splenomegaly, and severe cholemic nephrosis. The uterus was normal in size although soft. A yellow mass of tissue attached to the endometrium at the fundus represented a placental site. Cystic areas were observed in and beneath the mucosa of the vagina and the ectocervix. Focal superficial ul-

cers involved the vaginal mucosa and the submucosal blood vessels were moderately dilated.

CASE 4. The patient was a 46 year old white woman, para 4, gravida 9, who was admitted to the hospital complaining of severe shortness of breath. She gave a long history of chronic pulmonary disease and psychoneurosis and had been hospitalized on many occasions for these conditions. Dyspnea and cyanosis were moderately severe. The anterior-posterior diameter of the chest was increased, and the thorax was hyperresonant to percussion. The leaves of the diaphram were low and their excursion was decreased. Breath sounds were distant and accompanied by wheezes. The pulmonic second sound was greater than the aortic. The fingers were clubbed and the nail beds cyanotic. The patient became comatose, more cyanotic, and respirations ceased 4 days after admission.

The patient gave a history of a right salpingo-oophorectomy 24 years prior to admission and a vague history of an early carcinoma of uterine cervix treated with radium implants 17 years before the final admission. No pelvic examination was made on this admission but a previous examination had not revealed gross lesions.

Necropsy confirmed the presence of extensive pulmonary disease, chronic bronchiolectasis, emphysema, and fibrosis. The uterus was small and there were no corporal lesions. Many gas-filled cystic spaces were found beneath the mucosa of the vaginal face of the uterine cervix and the adjacent vaginal mucosa. No lesions were described by the prosector in the mid and lower portions of the vagina and tissue from these areas was not taken.

CASE 5. The patient was a white woman, 64 years of age, para 4. gravida 4, who was seen first in the Gynecologic Clinic on July 12, 1949. The only specific complaint was a slight brownish vaginal discharge during the previous few weeks. This appeared following injections of theelin which were given by her physician for general complaints of fatigue and weakness. Menopause had occurred 22 years previously and there had been no vaginal bleeding or discharge until the present episode. The patient was examined in the medical, neurological, and psychiatric clinics; the diagnoses were generalized arteriosclerosis and psychoneurosis of mixed type. A gynecologic examination revealed atrophic external genitalia. The mucosa of the vagina and the vaginal portion of the uterine cervix was rough and nodular but no cystic foci were described. The uterus was small, freely movable, and there were no adnexal masses. The clinical gynecologic diagnosis was senile vaginitis and a biopsy was performed in order to rule out the possibility of carcinoma.

The patient was admitted to the hospital for further investigation on July 26, 1949. At this time the mucosa of the vagina and cervix appeared smooth and the nodular areas which were previously described were not seen. Coned material was obtained however, from the uterine cervix and biopsies were taken from the vaginal wall. No specific lesions were found in this material and the patient was discharged. Repeat examinations were made at intervals of 6 months for 2 years and there was no recurrence of symptoms or lesions.

CASE 6. The patient was a white woman, 44 years of age, para 4, gravida 4, whose chief complaints on admission to the hospital were inability to have intercourse and a yellow vaginal discharge. The former complaint was noticed approximately 7 years before admission and was attributed by the patient to an unsuccessful attempt to induce an abortion by chemical means at the age of 27 years. Eight years ago a diagnosis of chronic rheumatic heart disease with mitral stenosis, atrial fibrillation, and congestive cardiac failure was made and the patient required careful supervision and treatment to prevent recurrent bouts of congestive cardiac failure. A pelvic examination on admission revealed normal external genitalia. Approximately 3 centimeters inside the introitus there was a constricted area with adhesions. Above this point the mucosa of the vagina was roughened and the wall thickened. Biopsies were taken to exclude neoplasm. After an interval of 7 days, the vagina was dilated under anesthesia and additional biopsies of the roughened areas were obtained which disclosed the same cystic lesions observed in the initial biopsies. The uterus was small and freely movable. No specific therapy was given, and the patient was discharged. An examination in the outpatient clinic 6 weeks after the patient was discharged from the hospital did not reveal recurrence of the lesions.

CASE 7. The patient was a white woman, 67 years of age, para 2, gravida 2, who was admitted to the hospital for the investigation of symptoms which were suggestive of cholecystitis. She also complained of a vaginal discharge which she had treated by daily douches. Menopause had occurred at the age of 52 years and there had been no bleeding or discharge until a short time before admission. Gynecologic examination revealed a small, freely movable uterus and there were no adnexal masses. The mucosa of the upper part of the vagina was roughened and cystic. No lesions were observed in the pars vaginalis of the uterine cervix. Multiple biopsies of the vaginal mucosa were taken to exclude carcinoma. No specific therapy was given and the patient was subsequently discharged from the hospital, the diagnosis being cholecystitis, obesity, and vaginitis.

CASE 8. The patient was a white woman, 47 years of age, para 1, gravida 2. She had had pulmonary tuberculosis for 18 years, but had enjoyed fairly good health until recent progression of her disease, which required transfer to the University Hospital for a left thoracoplasty. Because of a vaginal discharge and cessation of menses, a gynecologic examination was done prior to the first stage of the thoracoplasty. The

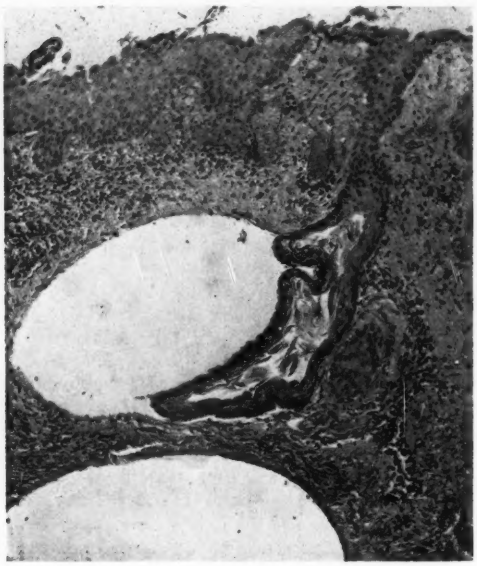

FIG. 1. Two recently formed cystic spaces in the substantia propria of the vagina. One is adjacent to, and appears to compress a mucosal invagination. Hyperplasia of mucosa and acute passive congestion and nonspecific inflammation of substantia propria. Hematoxylin and eosin stain, ×89.

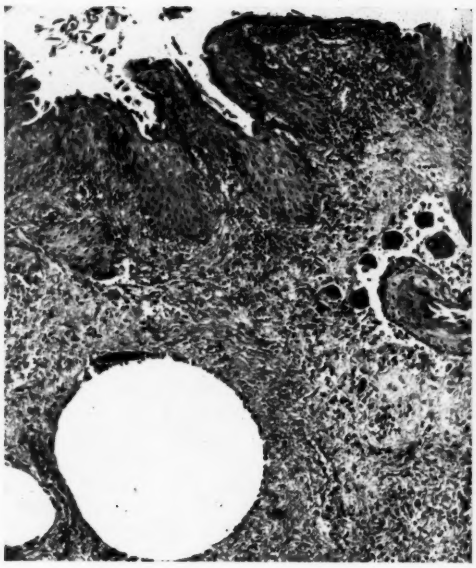

FIG. 2. Hyperplasia and invagination of vaginal mucosa. One recently formed cystic space with flattened multinucleated giant cells and a partially collapsed cystic space which contains giant cells of foreign body type. The latter space is adjacent to a mucosal invagination. Hematoxylin and eosin stain, ×74.

uterus was freely movable and there were no adnexal masses. No vaginal or cervical lesions were observed. Stilbesterol was prescribed and douches were given. A second gynecologic examination approximately 1 month later and after the final stage of thoracoplasty, revealed numerous raised vesicles from the introitus to the cervix and also involving the right lip of the cervix. There were no ulcers. Multiple biopsies of the vaginal mucosa were done. The patient, having made a good recovery from the surgical procedure, was discharged from the hospital and no further gynecologic examinations were made.

MICROSCOPIC FINDINGS

The 4 examples of cervicocolpitis emphysematosa which were diagnosed at necropsy provided abundant material for detailed study. In each of the 4 cases, the vaginal portion of the uterine cervix and the vagina were involved. There was no involvement of the endocervical or corporal portions of the uterus and no evidence of either pneumatosis intestinalis or cystitis emphysematosa. The lesions in the examples diagnosed by biopsy were similar but because of restricted amounts of tissue were less valuable in assessing the different features.

Optically clear cystic spaces throughout the substantia propria are the hallmark of this condition and were present in all cases (Figs. 1 to 4). These tended to occur in clusters and sometimes had a multiloculated appearance. No endothelial or epithelial lining could be demonstrated in the cystic lesions, and they were interpreted as focal accumulations of a gas in the connective tissues. Some were immediately beneath the mucosa and others were adjacent to epithelial invaginations (Figs. 1 and 3). The squamous epithelium of the invaginations often appeared compressed or forced into crescentic configurations about the walls of the cystic spaces (Fig. 1). The lesions which were thought to be recent appeared under some tension with compression of adjacent stroma. Collapsed spaces

FIG. 3. Multiple cystic spaces beneath the squamous mucosa of the vaginal portion of the uterine cervix near the fornix. Several compressed giant cells are in the walls of the tissue spaces. Hematoxylin and eosin stain, ×50.

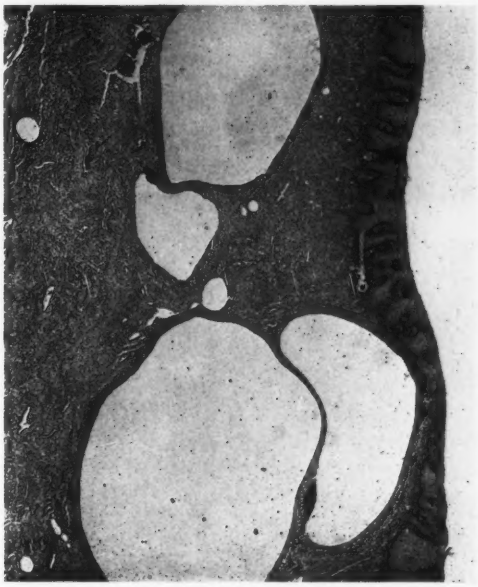

FIG. 4. Photomicrograph illustrating multiple recently formed cystic spaces which were present beneath the mucosa of the uterine ectocervix. Hematoxylin and eosin stain, ×26.

possessed irregular outlines often slit-like in shape and sometimes surrounded by a thickened and homogenized stroma (Fig. 6). Defects in adjacent mucosa suggested that some cysts might have discharged their contents into the vaginal lumen. No inflammation or giant cell reaction was present in the stroma about the gas spaces which were considered to be recent, but there were accumulations of lymphocytes, plasmacytes, mononuclear cells, and elongated multinucleated giant cells of the foreign body type about the older, but still cystic lesions (Figs. 2 and 3). The giant cells were most numerous in the collapsed or partially collapsed spaces where they were rounded rather than elongated or crescentic (Fig. 6). A few inflammatory cells and some protein fluid were also present in these spaces. There was no evidence of origin of the giant cells from squamous epithelium and they appeared to be histiocytic in derivation. Some contained phagocytized debris.

Hyperplasia of the squamous mucosa was marked and somewhat verrucose in 3 patients (Figs. 1, 2, and 5); there were many invaginations and solid downgrowths of epithelium. Marked desquamation and exfoliation of epithelial cells suggested a loss of normal cohesiveness (Figs. 2 and 5). In a few areas the mucosal epithelium was absent or the vaginal lumen was separated from the congested substantia by 1 to 3 layers of epithelial cells. Some of the invaginations contained desquamated cells and others were adjacent to underlying cystic spaces (Figs. 1, 3, and 5). Vascular dilatation of capillaries and venules beneath the mucosa was focally prominent and occasional veins contained hyaline thrombi. Veins and lymphatics deep in the vaginal wall were also dilated. Some of the lymphatic channels were so dilated and devoid of content that it was sometimes difficult to separate them from cystic tissue spaces and the presence of gas within the vessels could

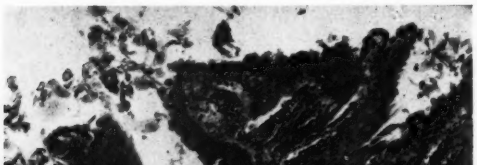

FIG. 5. Hyperplasia and superficial desquamation of cells of vaginal mucosa with several invaginations. Chronic nonspecific inflammation of substantia propria. Hematoxylin and eosin stain, ×96.

not be excluded. Accompanying the submucosal congestion was a nonspecific inflammatory infiltrate of variable intensity consisting of lymphocytes, plasmacytes, and a few neutrophils, eosinophils, and mast cells. No organisms were demonstrated in the tissues.

DISCUSSION

Small "gas spaces" grouped beneath the raised and usually hyperplastic squamous mucosa of the vagina and vaginal face of the uterine cervix, and the foreign body reaction that their contents excite, are pathognomonic of cervicocolpitis emphysematosa. The "bladders" may break with an audible "pop" and the process has been likened to the breaking of toy balloons. They vary from a few millimeters to 2 centimeters in diameter. Involvement has been restricted to the vagina and uterine cervix except for 1 report of vulvar lesions. Symptoms, when present, are not severe and consist of slight vaginal discharge or a feeling of pressure within the vagina. Occasionally the cystic lesions must be ruptured to relieve the feeling of pressure and discomfort. The condition resolves spontaneously and usually does not recur although Robberson and Owen reported a case in which the lesions occurred twice within a period of 2 years.

Lesions which are microscopically similar to those described in this article have been observed in the small intestine, pneumatosis intestinalis, and in the urinary bladder, cystitis emphysematosa, and have been produced experimentally in the subcutaneum. Involvement of one system by this type of reaction is not usually associated with involvement of one of the others.

Some investigators have claimed success in culturing gas-producing organisms from the vaginal lesions and in demonstrating organisms in the microscopic sections, but others have not been able to confirm these results. The analysis of gas from vaginal lesions and from similar intestinal lesions suggests that it is air and this observation is against a bacterial origin. Attempts to produce vaginal lesions in animals and in a human volunteer by the use of vaginal secretions and washings of the gas spaces have failed. No bacteria were demonstrated in the tissues of the cases of this study. Thus, although the possibility of an infectious origin cannot be excluded with complete assurance, the available evidence indicates that the gaseous vesicles are not the direct result of bacterial action.

The gas-filled spaces have been considered to be dilated lymphatic channels, cystic epithelial invaginations, and cystic supportive tissue spaces. We could find no evidence to discount the latter view supported by Ingraham and Hall. The lymphatic channels were dilated but it was not possible to confirm that they contained gas, as has been suggested. Although many of the cystic areas were closely related to the mucosal downgrowths and invaginations, they were not lined by demonstrable epithelium.

The multinucleated giant cells, which were structurally different from the giant

cells of so-called giant cell vaginitis, were not associated with the tense recently formed cystic spaces, but became prominent as the "gas" in the spaces was absorbed. Initially, the giant cells were elongated or crescentic but as the amount of gas in the spaces decreased, they became round or oval. They were numerous in and about the cleft-like slits which represented collapsed lesions. This interpretation is opposite to that of Buckingham and McClure who considered the giant cells to have appeared prior to the appearance or formation of the gas. Bender and Jeffcoate suggested that the giant cells were derived from downgrowths of vaginal mucosa. The staining reactions, the phagocytic powers, and the structure of these cells, however, support a histiocytic origin as maintained by Ingraham and Hall. Similar foreign body giant cells have been observed by Wright as a reaction to gases, especially nitrogen and oxygen, injected subcutaneously into animals.

The available evidence indicated that under certain predisposing conditions and by some means, air is forced into the wall of the vagina and initiates a foreign body response. What are the factors, local or general, which may predispose to the development of this lesion? Nagashima considered local circulatory disturbances leading to stasis of blood and lymph as an important factor. The frequent occurrence of the disease in pregnancy could readily be explained on this basis. Four patients in this series had chronic congestive cardiac failure, and 2 had systemic congestion secondary to chronic pulmonary disease and reduced pulmonary reserve. This association of the two conditions would seem to be of definite significance. Estrogenic therapy and hot vaginal douches may have induced some degree of local congestion in the 2 other patients. Histologic evidence of marked congestion or hyperemia beneath the mucosal epithelium was present in 7 cases and in some areas it was almost telangiectatic in nature. What importance the congestion or hypoxia plays is not known. In patients

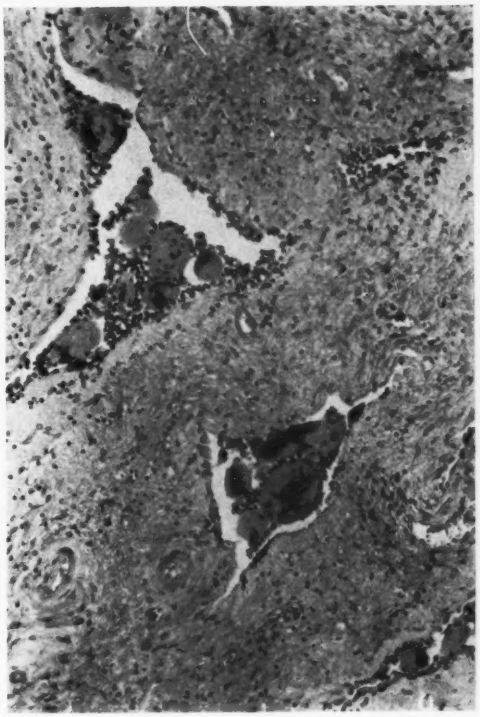

FIG. 6. Multinucleated giant cells of foreign body type within partially collapsed cystic spaces in substantia propria of vagina. Hematoxylin and eosin stain, ×121.

with cardiac failure and hypoxia, the mechanism of respiration may be so altered as to favor the aspiration of air into the vagina whence it is forced or escapes into tissues beneath the mucosa.

A prominent histologic feature in the cases at necropsy was the associated hyperplasia of the vaginal mucosa which was almost verrucose in nature and associated with an exfoliation or desquamation of superficial cells suggesting a loss of cellular cohesiveness. Although present to some degree in the other cases, it was not a prominent feature. Others have noted its presence, but not in all instances. Ingraham and Hall considered significant hyperplasia to be present in only 1 of 3 cases that they reported. In some areas where the mucosa had a verrucose arrangement, the lumen was

separated from the congested stroma by only 1 to 3 layers of cells.

The site of entrance of the gas into the wall of the vagina could not be definitely identified. Several tears in the mucosa were visible but could have represented points of rupture of cystic lesions into the lumen. Some workers believe the point of entrance of gas to be in the invaginations. It was concluded that the changes in the mucosa may have preceded the appearance of the cystic lesions and possibly were part of a process which allowed air to more readily penetrate into the wall. What induces these changes is not known. Passive congestion with hypoxia, either as part of systemic congestion in congestive cardiac failure or secondary to local disturbances associated with pregnancy, certainly appears to predispose to the development of the condition.

In 2 of the 4 lesions demonstrated at necropsy, the patients had had vaginal examinations 2 weeks and 1 month prior to death and no lesions were seen, the vaginal and cervical mucosa being described as smooth and glistening in each instance. One patient in whom the diagnosis was made by biopsy had a negative vaginal examination 1 month previously. In 2 patients, clinical examinations and biopsies, 2 and 6 weeks respectively after the original diagnoses, did not disclose any cystic lesions or the presence of giant cells. It thus appears that the condition is usually of short duration and that the gas can be absorbed fairly rapidly, possibly by lymphatic channels, with return of tissues to a normal appearance unless additional gas enters the stroma as probably occurs during pregnancy.

SUMMARY

Eight cases of cervicocolpitis (vaginitis) emphysematosa are reported. None of the examples occurred in pregnant women; 4 occurred in women after the menopause. A predisposing condition in 4 patients was congestive cardiac failure and in 2 other patients there were systemic congestion and hypoxia which were associated with chronic pulmonary disease.

The characteristic feature of the disease is the presence of cystic lesions, "gas spaces," in the connective tissue beneath the mucosa of ectocervix and vagina. These "gas spaces" are presumed to contain air and excite a foreign body reaction with multinucleated giant cells. Other histologic changes include marked congestion of submucosal tissues, exfoliative hyperplasia of squamous mucosa, and chronic inflammation. There is no evidence that the condition is due to any specific infective organism.

The lesions appear to form quickly, disappear just as readily, and do not tend to recur except possibly during pregnancy.

The observation of 8 cases during a period of 17 years indicates that the condition is not as rare as reports in the English literature would suggest.

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THE ROLE OF ANGIOCARDIOGRAPHY IN THE SURGICAL TREATMENT OF MASSIVE PERICARDIAL EFFUSIONS

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THE DIAGNOSIS of pericarditis with effusion, even when massive, is difficult. Physical, electrocardiographic, and conventional roentgen examinations may fail to establish the presence of pericardial fluid. Angiocardiography, however, by outlining the cardiac chambers, permits recognition of adjacent pericardial fluid.

More and more, pericardiectomy is being advocated for diagnosis and treatment of chronic pericardial effusions. Five patients with massive pericardial effusions herein reported recovered promptly following decompression, drainage, and partial pericardiectomy. The importance of angiocardiography in the diagnosis of pericarditis with effusion is also illustrated.

REPORT OF CASES

CASE 1. A 68 year old housewife was admitted to the hospital on December 5, 1951, complaining of generalized edema. Two weeks before admission, a sudden pain in the right axilla occurred. Four days later, generalized edema became evident. On physical examination, the blood pressure was 155/75 millimeters of mercury; the venous pressure was 50 millimeters of saline. There was pitting edema of ankles and back. Rales were present at the bases of the lungs and the heart sounds were faint. A systolic (grade 2) murmur was heard at the base. The area of cardiac dullness was widened. The laboratory data were normal except for the electrocardiogram which showed low amplitude. The roentgenograms of the chest revealed massive enlargement of the cardiac silhouette in all diameters (Fig. 1a and b). In frontal view (Fig. 1a), the right border of the cardiac silhouette almost reached the right lateral chest wall and because of the asymmetry, a pericardial or mediastinal tumor was suspected. Angiocardiography on December 13, 1951, however, showed a massive pericardial effusion with accumulation of fluid anteriorly and retrosternally with the fluid being also lateral and inferior to the heart, which was displaced posteriorly (Fig. 1 c, d, e, and f).

Twelve days after admission, operation through a right thoracotomy disclosed a large pericardial effusion. The pericardium was about twice the normal thickness, but the heart, lungs, and pleural cavity were normal. The pericardium was drained and closed loosely, a catheter being placed in the right side of the chest for drainage. The patient tolerated the procedure exceedingly well and the postoperative course was uneventful; the roentgenogram showing a normal cardiac silhouette (Fig. 1g). She was discharged in good condition 15 days after operation.

CASE 2. A 66 year old housewife was admitted to the hospital on July 15, 1955, because of weakness and chest pain of 6 weeks' duration. She had been in good health until the onset of constricting chest pain, 6 weeks before admission. Five weeks earlier she had been admitted to another hospital for "heart failure and atrial fibrillation." Prior to admission to The New York Hospital, retrosternal and precordial pain associated with weakness developed. Physical examination showed distended neck veins and scattered wheezes throughout the lung fields. The cardiac area was enlarged to percussion and the heart sounds were faint; the rhythm was regular. The liver was slightly enlarged and tender. The blood pressure was 124/74 millimeters of mercury; the circulation time (decholin) was 17 seconds; and the venous pressure was 135 millimeters of saline. There was no peripheral edema. The laboratory findings were normal except for low amplitude in the electrocardiogram.

The roentgenogram of the chest showed massive enlargement of the cardiac silhouette in all diameters, in this instance, chiefly toward the left lateral chest wall (Fig. 2a) and retrosternally (Fig. 2b). Again, the unusual roentgen configurations suggested either a pericardial or mediastinal tumor. Angiocardiographic examination on July 12, 1955, however, disclosed massive pericardial effusion with displacement of the heart posteriorly (Fig. 2 c, d, and e).

On July 26, 1955, the left side of the chest was opened through an anterior approach. The pericardium was purplish, thickened, covered with dilated vessels, and bulged into the wound. A large amount

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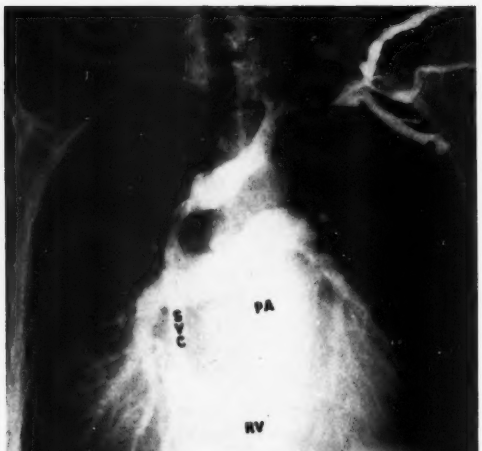
a

b



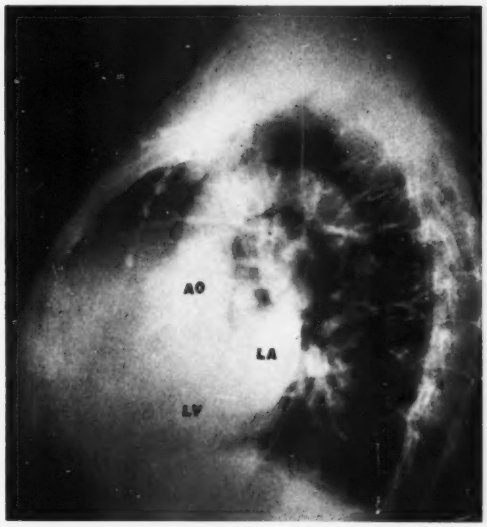
c

d

of chocolate-brown fluid was slowly aspirated, and after gradual decompression the pericardium was incised. Its internal surface was granular and a shaggy epicardium was covered with mucous shred-like material. The fat about the coronary vessels was edematous and contained many small punctate hemorrhages. The heart was of normal size and there was no evidence of tumor. A generous portion of pericardium was removed and a tube was placed in the left pleural cavity for drainage. The patient tolerated the procedure well but the heart was irritable; frequent extrasystoles and arrhythmia developed whenever the heart was palpated. The postoperative course was again uneventful and the patient was discharged, asymptomatic and in good condition, 23 days following operation.

Case 3. A 53 year old housewife was admitted to the hospital on April 7, 1954, with the complaint of dyspnea of 5 weeks' duration. She had had hypertension as high as 250 millimeters of mercury for 35 years and enlargement of the heart for 10 years. Ankle edema and three pillow orthopnea had been present for 30 years, while anginal pain on exertion had also occurred for 6 years. Five weeks prior to admission, sudden increase of dyspnea and weakness developed.

e



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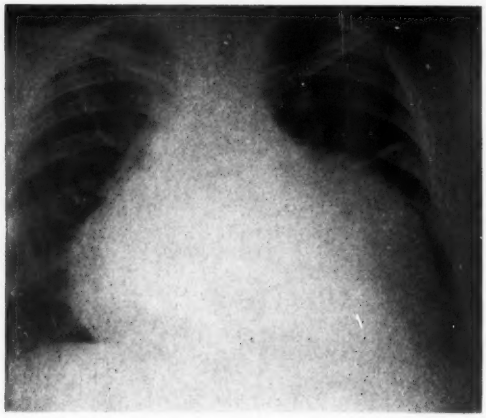
g

FIG. 1. Case 1. a, Frontal teleoroentgenogram shows a huge cardiac silhouette, mostly of the right border. Old calcific tubercles are present at the left base. b, Lateral roentgenogram shows obliteration of the retrosternal space. c, Frontal angiocardiogram reveals the superior vena cava (*SVC*), right atrium (*RA*), right ventricle (*RV*), pulmonary artery (*PA*), and branches to be opacified. Note the pericardial fluid beyond the right atrium. d, Frontal angiocardiogram showing opacification of the structures of the left side of the heart; left atrium (*LA*), left ventricle (*LV*), and aorta (*AO*). Note the pericardial fluid beyond the left ventricle. e, Lateral angiocardiogram shows the structures of the right side of the heart, the superior vena cava (*SVC*), right atrium (*RA*), right ventricle (*RV*), pulmonary artery (*PA*), and branches to be opacified. Note the retrosternal pericardial effusion. f, Left lateral angiocardiogram reveals the left atrium (*LA*), left ventricle (*LV*), and aorta. Note that the left atrium forms the posterior border of the heart, the pericardial fluid being anteriorly and inferiorly to the heart. g, Postoperative roentgenogram of the chest showing the normal cardiac silhouette. There is obliteration of the right costophrenic sulcus.

Physical examination revealed inconstant moist rales at the bases. The cardiac area was markedly increased, the dullness extending to the left anterior axillary line. A soft apical (grade 1) systolic murmur was elicited. The blood pressure was 190/94 millimeters of mercury. Liver dullness extended 2 finger breadths below the costal margin and there was marked pitting edema of both legs. The roentgenograms of the chest showed a huge cardiac silhouette, the left contour reaching the axilla (Fig. 3a), while in lateral view there was marked filling of the retrosternal space. Here, too, the long duration of symptoms, hypertension, edema, angina, and dyspnea suggested cardiac failure with dilatation and enlargement of the heart. Angiocardiography, however, showed massive pericardial effusion (Fig. 3b).

At operation a huge pericardial effusion containing blood was found. After slowly decompressing the pericardium, it was widely opened, a piece being excised for biopsy. A tube was then placed in the left side of the chest for drainage. The patient tolerated the procedure well and improvement in color oc-



a

c

b

FIG. 2. Case 2. a, Frontal teleorentgenogram shows a huge cardiac silhouette, the enlargement being mostly along the left border. b, Lateral x-ray film shows complete obliteration of the retrosternal space. c, Frontal angiocardiogram shows lateral displacement of the superior vena cava to the right side. The right atrium (*RA*), right ventricle (*RV*), pulmonary artery (*PA*), and branches are seen. Note the large pericardial effusion on the right (pericardial border outlined by arrows). d, Lateral angiocardiogram also shows anterior displacement of the superior vena cava. The right atrium (*RA*), pulmonary artery (*PA*), and branches are opacified. e, Lateral angiocardiogram reveals the structures of the left side of the heart; left atrium (*LA*), left ventricle (*LV*) and aorta (*AO*). Again, note the retrosternal pericardial fluid; the structures of the left side of the heart, pulmonary veins, left atrium, and aorta are not surrounded by fluid posteriorly. Note also that the pericardial fluid is retrosternal and infracardiac.

curred soon after the pericardium was drained. The patient's postoperative course was poor for 3 to 4 days but then gradually improved and she was discharged in good condition, 14 days following operation.

CASE 4. An 11 year old Egyptian schoolboy was admitted because of the finding of "an enlarged heart" following a mild upper respiratory infection 10 months earlier. Despite absence of symptoms and fever, he was suspected of having rheumatic heart disease, given hormonal treatment, and for almost a year kept at bed rest. When after all this time the cardiac shadow remained large and unchanged, he was brought to the United States where angiocardiography for diagnosis was advised.

Physical examination showed good nourishment and development. The lungs were clear. There were no cardiac murmurs and the blood pressure was 106/60 millimeters of mercury; the venous pressure was normal. The liver edge was nontender but extended 3 centimeters below the costal margin Laboratory data revealed normal blood studies and erythrocyte sedimentation rates. The tuberculin test was negative and electrocardiographic studies showed only low voltage. The roentgenogram of the chest revealed a huge cardiac silhouette (Fig. 4a). Angiocardiography established the presence of a massive pericardial effusion (Figs. 4b and c).

On August 9, 1956, a left anterior thoracotomy revealed a greatly distended pericardium which bulged into the wound. About 1,000 cubic centimeters of

d

e

milky fluid were slowly aspirated. A generous portion of pericardium was resected and a tube was inserted for drainage. The patient tolerated the procedure exceptionally well and convalescence was without incident. After release of pericardial fluid, immediate increase in the voltage of the electrocardiogram resulted. He was discharged from the hospital after 10 days. Three weeks after operation, the liver edge could no longer be felt. A variety of studies of the pericardium and fluid failed to establish the cause of the effusion.

CASE 5. A 67 year old housewife was first seen in 1942 with a classical history of myxedema; the basal metabolic rate was −34. At that time the cardiac silhouette appeared enlarged and 50 cubic centimeters of straw colored pericardiac fluid were aspirated. She was treated for hypothyroidism and was well until December 1956, when she complained of dyspnea and ankle edema. The physical examination showed the patient to be in respiratory distress preferring to sit erect. There were grade 2 systolic pericardial murmurs; the blood pressure was 145/65 millimeters of mercury.

Roentgen examination of the chest (Figs. 5a and b) showed a tremendous cardiac silhouette, the left border reaching the axilla. Soon after, pericardial thoracentesis yielded 400 cubic centimeters of bloody fluid. This was replaced by air (Fig. 5c and d). Subsequently, the patient developed a left pleural effusion and on 2 occasions 500 cubic centimeters of bloody fluid were secured by tapping the left chest.

Considerable relief of symptoms followed these procedures but gradual reaccumulation of the pericardial fluid resulted in readmission to the hospital. On April 4, 1957, the chest was opened through a left thoracotomy and massive bloody pericardial fluid was drained with a pericardial pleural window defect being established. The patient had an uneventful postoperative course and was discharged 11 days after operation. Studies of the pericardium and fluid failed to establish the etiology of the effusion.

DISCUSSION

Although fatalities from conservative treatment of pericardial effusions are uncommon, the exceptional results of surgery in the cases presented are strong arguments for this form of therapy. Furthermore, the operation may be the only way to establish the etiology of the effusion, and, especially in the case of tuberculosis, permit specific treatment without delay. Also, in tuberculous pericarditis, study of the aspirated fluid (smear, culture, and guinea pig inoculation) may be negative, whereas culture and microscopic examination of the biopsied pericardium may establish the diagnosis. Unfortunately, despite operation and extensive investigation of the fluid and pericardium, the etiology often remains obscure. Operation will, however, exclude infection and trauma from the differential diagnosis.

In only 1 patient in the series was a likely etiology of the pericardial effusion estab-

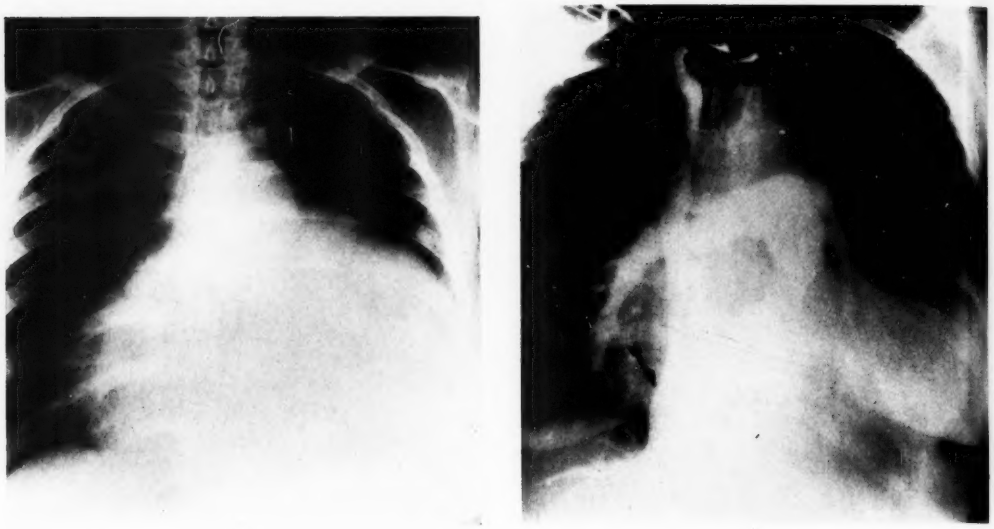


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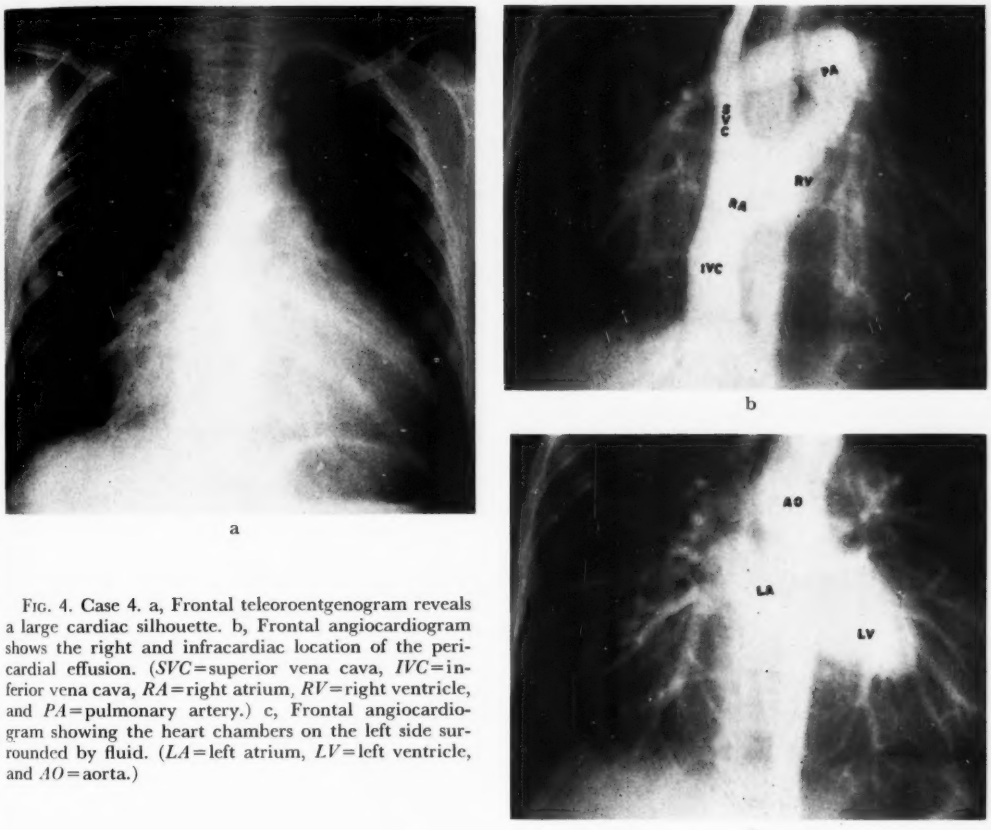
FIG. 3. Case 3. a, Frontal teleoroentgenogram showing a huge cardiac silhouette. b, Frontal angiocardiogram shows the large pericardial effusion beyond the opacified right atrium (arrow).

lished preoperatively (Case 2). This patient had had a history of being in good health until 6 weeks prior to admission when sudden dyspnea, chest pain, and swelling of the neck veins developed. After questioning, however, she recalled having been in an automobile accident 2 months earlier and striking the thorax so hard that "all the wind was knocked out." Because of the bloody fluid, trauma is believed to have caused the chronic pericardial effusion in this instance. Initially, intrapericardial hemorrhage probably acted as an irritant and resulted in massive pericardial effusion and tamponade. However, chronic hemorrhagic pericarditis may occur without trauma, Effler and Proudfit having reported 8 such cases.

The difficulties in establishing a diagnosis of pericardial effusion are illustrated in Case 3; the long duration of cardiac symptoms made it difficult to evaluate the significance of increased disability due to the pericardial effusion.

There is no general agreement as to the value of pericardial paracentesis for diagnosis and treatment of chronic pericardial effusions. However, pericardial tapping is contraindicated if the diagnosis rests between a pericardial cyst and an effusion, since the character of the fluid is not significant diagnostically and drainage will not prevent reaccumulation of fluid. Furthermore, an exploratory operation is advisable whenever mediastinal tumors are suspected because extirpation of the mass, whether cystic or solid, is curative.

Operation is also indicated for recurrence or persistence of effusions after pericardiocentesis. Repeated aspirations of the pericardium are hazardous and seldom lead to cure. For instance, in Case 5, a 69 year old woman who had had myxedema for 15 years, a massive pericardial effusion developed. Removal of blood-tinged fluid gave immediate relief but the effusion recurred shortly with the return of dyspnea, orthopnea, and edema of the extremities. In order to establish the etiology of the effusion, exploratory pericardiectomy was advised. At operation the pericardium was found to be greatly distended by brown-colored fluid, but it was smooth and only slightly thicker than normal. The heart was normal in size and



a b c

FIG. 4. Case 4. a, Frontal teleoroentgenogram reveals a large cardiac silhouette. b, Frontal angiocardiogram shows the right and infracardiac location of the pericardial effusion. (*SVC*=superior vena cava, *IVC*=inferior vena cava, *RA*=right atrium, *RV*=right ventricle, and *PA*=pulmonary artery.) c, Frontal angiocardiogram showing the heart chambers on the left side surrounded by fluid. (*LA*=left atrium, *LV*=left ventricle, and *AO*=aorta.)

appearance. A portion of pericardium was removed for biopsy and the patient made an uneventful recovery. Although study of fluid and pericardium failed to establish the etiology of the pericarditis, it excluded tuberculosis and obviated prolonged drug therapy.

Failure to establish a diagnosis of pericardial effusion may not only delay treatment but result in prolonged and often unnecessary treatment. This is illustrated by Case 4 in which the patient primarily came to this country for diagnosis and treatment of "an enlarged heart." Eleven months before, a roentgenogram of the chest had revealed an enlarged cardiac silhouette and even though the patient was asymptomatic, a diagnosis of pancarditis was made. He received streptomycin, other antibiotics, and cortisone. Nine months of needless bed rest was given before the diagnosis of pericarditis with effusion was established (Fig. 4b and c). At operation because of the chylous character of the pericardial fluid, the thoracic duct was explored but appeared intact and any relation to the pericardium could not be established. There appears to be general agreement that surgical drainage and the establishment of a pleural pericardial window constitute the treatment of choice. Other methods for diagnosis of chylous pericarditis suggested recently by Madison and Logue were not, however, carried out.

Surgical drainage and partial pericardiostomy have proved so very satisfactory that this procedure is recommended for the treatment of all patients with chronic mas-

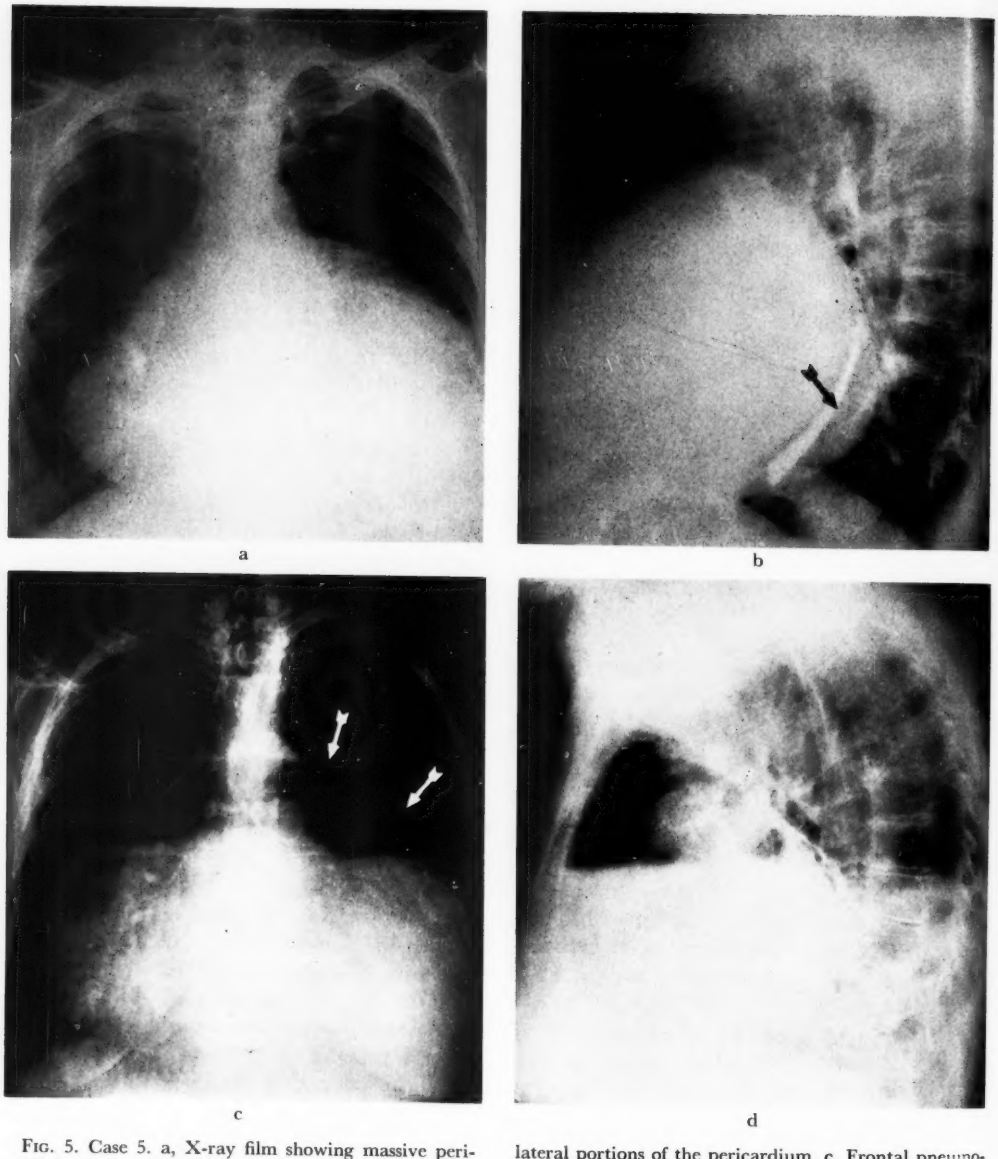


FIG. 5. Case 5. a, X-ray film showing massive pericardial effusion, especially in the left hemithorax. b, Lateral esophagram showing obliteration of the retrosternal space. Note that beyond the esophagus (arrow) there is pericardial effusion due to distention of the lateral portions of the pericardium. c, Frontal pneumopericardial x-ray film. Arrows show the border of the left upper part of the pericardium. d, Lateral pneumopericardial x-ray film clearly demonstrates the retrosternal and anterior location of the pericardial effusion.

sive pericardial effusions. The ideal approach is through the fourth left interspace anteriorly which also provides adequate exposure and allows placing the patient in the position of maximal respiratory efficiency. The pericardial sac should be decompressed slowly, and, once emptied, part of it should be removed to prevent the possibility of con-

strictive pericarditis. Also, the pleural cavity should be drained. Convalescence following surgery can be expected to be without incident. All patients in our small series have shown no evidence of recurrence for a period varying from 1 to 6 years, an experience duplicated by the other reports in the literature.

Observations following angiocardiography in patients with pericarditis with effusion reveal that pericardial effusions first begin in the infracardiac, diaphragmatic portion of the pericardium. As fluid increases, the retrosternal pericardial space is filled and can often be recognized by eliciting dullness over the sternum. In pericardial effusions, the heart is surrounded by fluid (Figs. 1c and d, 2c, 3b, 4b and c) except posteriorly, where pericardial reflections over the inferior vena cava below and the pulmonary veins, pulmonary artery, and aorta above prevent accumulation of fluid (Figs. 1e and f, 2d and e). Because of the retrosternal pericardial accumulation of fluid, the blood-filled cardiovascular structures are forced backward, compress the lung and bronchi, and are responsible for Ewart's sign (3). In massive pericardial effusions, marked distention of the lateral pericardial pouches occurs and behaves like inflated water wings, causing additional compression, thus enhancing Ewart's sign. Figure 5b illustrates the laterally distended pericardial recess showing beyond the posterior cardiac border. Figure 5d illustrates the retrocardiac position of pericardial effusions. Pericardial paracentesis through the posterior approach when made low in the thorax yields fluid either from the infracardiac pericardial space or from the distended lateral pericardial pouches. In order to avoid traversing lung, the anterior route in the region of the xiphoid or apex of the heart is recommended for pericardial paracentesis.

SUMMARY AND CONCLUSIONS

Five patients with massive pericardial effusions were treated by incision and drainage of the pericardium. Recovery of the patients was prompt and there was no recurrence of the effusion. Cultural and biopsy studies of the pericardium and fluid were not helpful in establishing the etiologies of the effusion. In 3 instances the effusions contained blood but only 1 patient had a history of antecedent trauma to the chest. The cause of a chylous pericarditis in 1 patient could not be determined despite exploration of the thoracic duct.

In 4 patients with massive pericardial effusions the diagnosis was difficult; angiocardiography established the presence of pericardial fluid and excluded mediastinal and pericardial masses. Angiocardiography also proved helpful for the understanding of the bizarre appearance of the contours of the cardiac silhouette in massive pericardial effusions.

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RESULTS OF CONSERVATIVE MANAGEMENT OF CANCER OF THE RECTUM IN POOR RISK PATIENTS

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AT THE PRESENT TIME, radical surgical procedures offer the patient with cancer of the rectum the best chance for a curative result. However, despite progress in the fields of anesthesia, surgical technique, and preoperative and postoperative care, some patients are unable to tolerate such formidable operations; and others refuse to submit to radical operations. Good judgment on the part of the clinician and surgeon dictates that certain patients with associated cardiovascular disease, senility and general disability, severe hypertension, diabetes, and so on, be managed by conservative methods. Crile (1) and others have pointed out that surgeons frequently must choose between a simple operation that is relatively safe and a more extensive one with a higher mortality and morbidity.

This study was undertaken because we so often were surprised at the apparent attainment of good results by conservative methods in some of these poor risk patients as observed on return visits years after treatment. To find out about the further course of a group of these conservatively treated patients with cancer of the rectum, we studied the records of all of those managed in this manner at the Mayo Clinic in the 5 year period from January 1, 1945 through December 31, 1949. The resultant series was comprised of 128 cases in which normally some type of radical surgical treatment would have been applied, but in which, because of some associated debilitating condition or refusal of the patient to submit to radical procedures, the clinician and surgeon had decided that some less drastic procedure was to be employed. In the 5 year period under consideration, approximately 1,900 additional patients underwent some form of radical surgical treatment for carcinoma of the rectum, so that the series of 128 managed conservatively actually represents only about 6 per cent of the total cases.

Excluded from this study were those patients whose lower bowel lesions, such as pedunculated and sessile adenomatous or in situ adenocarcinomatous lesions, would normally have been treated by conservative methods. Also excluded are those who either refused or were found unsuited for all treatment of whatever kind.

These 128 patients were managed by what are usually considered to be conservative or palliative methods, consisting of fulguration, irradiation (either by radium or by roentgen rays), or local excision, or combinations thereof.

Eighty-one of the patients were men and 47 were women. The youngest patient was 32 years old and the oldest was 84 at the time of treatment. When this study was made, 53 of the patients were living and 75 were dead.

Survival is tabulated in Table I. It is noteworthy that after exclusion of the 12 patients who were still living but had not reached the end of the statistical 5 year follow-up period, 54 (46 per cent) of the 116 remaining had lived 5 years or more after conservative treatment and 6 had lived 10 years or more.

The principal reason for conservative treatment in each case was as follows: senility and general disability in 39 cases, patient's

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refusal 30, cardiovascular disease 28, metastatic lesions 19, diabetes 3, arthritis 2, cirrhosis of liver 2, alcoholism 1, carcinoma of bladder 1, carcinoma of breast 1, Hodgkin's disease 1, and mediastinal tumor 1. Actually, in a considerable number of instances not just one but rather a combination of factors increased the risk of surgical intervention. It will be noted that in 39 patients senility and general disability were the causes for conservative treatment. Several in this group had associated cardiovascular disease or demonstrable occurrences of metastasis. (The reader should bear in mind that some of these poor risk patients who were disqualified for radical operation a decade ago very likely would be acceptable now because of improved techniques and safer preoperative and postoperative therapy.)

Many reasons were given by the 30 patients who refused radical operation—"dread of colostomy," "not many years to live anyway," and the like.

Biopsy tissue was graded after Broders' method in all but 2 cases. As indicated in Table II, 62.5 per cent of the lesions were adenocarcinoma, grade 1, and 24.2 per cent more were adenocarcinoma, grade 2. In this particular study, we have made no attempt to correlate the survival time with the grade of the lesion. However, it is interesting to note that out of a total of 7 patients who had adenocarcinomas of the rectum graded 3 and were treated conservatively, 3 were living and well at the end of 5 years and 4 were dead.

The nature of the conservative treatment carried out was as follows: fulguration in 28 cases, local excision 19, irradiation (radium) 50, irradiation (roentgenologic) 3, fulguration and radium treatment 18, fulguration and excision 2, excision and radium treatment 6, and radium and roentgenologic irradiation 2. Most of the patients were treated by irradiation with radium, fulguration, a combination of the two, or local excision. Because of obstructive symptoms developing later, it was necessary subsequently to perform colostomies in 10 cases.

TABLE I.—RANGE OF SURVIVAL PERIODS

	Patients		
Years	*Living*	*Dead*	*Total*
<1	3	19	22
1	6	12	18
2	1	11	12
3		7	7
4	2	13	15
(Subtotal)	(12)	(62)	(74)
5	6	8	14
6	3	3	6
7	11		11
8	9		9
9	8		8
(Subtotal)	(37)	(11)	(48)
10+	4	2	6
Total	53	75	128

TABLE II.—DISTRIBUTION OF PATHOLOGIC GRADES (BRODERS) AND TYPES

Grade 1	
Adenocarcinoma	80
Grade 2	
Adenocarcinoma	31
Grade 3	
Adenocarcinoma	7
Squamous cell epithelioma	3
Grade 4	
Adenocarcinoma	3
Squamous cell epithelioma	2
Not graded	
Basaloid small cell carcinoma	1
Other	1
Total	128

TABLE III.—CAUSE OF DEATH IN EACH CASE

Causes	*No. of cases*
Carcinoma	
Rectal	21
Mammary	1
Probable	9
Other	
Cardiovascular disease	10
Cerebrovascular accident	3
Pneumonia	3
Senility	3
Brain tumor	1
Hodgkin's disease	1
Pyelonephritis	1
Traffic accident	1
Unknown	21
Total	75

Although the nature of the conservative treatment has to be individualized in accord with several factors, it has been our impression that fulguration immediately followed by the topical application of a radium pack has been the most satisfactory.

Of the 75 patients in the group who were dead at the time of this study, 21 had died as a result of the rectal carcinoma or com-

plications thereof, and carcinoma was the probable cause of death in an additional 9 cases (Table III). In 21 cases the cause of death could not be determined. So far as we could learn, 23 other patients died of conditions entirely unrelated to the rectal carcinomas.

COMMENT

When one considers the morbidity and mortality associated with the radical surgical treatment in certain poor risk patients with carcinoma of the rectum, it seems good clinical judgment to offer them the benefit of conservative treatment. Although this is sometimes spoken of as "palliative treatment," in our opinion, it is curative in more instances than is generally appreciated. That 54 of a series of 116 patients were living more than 5 years after the initial conservative treatment, that 6 were living more than 10 years later, and that 24 of the 75 deaths were unrelated to the rectal carcinoma has led us to believe that many of these poor risk or refusal patients can be salvaged by conservative methods.

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OBSERVATIONS ON THE RELATIONSHIP OF BENIGN ADENOMATOUS POLYPS OF THE COLON TO THE NATURAL HISTORY OF COLONIC CANCER

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IN A RECENT STUDY of the biogenesis of adenomatous polyps of the colon and rectum Valdes-Dapena and Beckfield called attention to the fact that one of the earliest histologic changes noted in polyp formation was thickening of the submucosa underlying the focus of mucosal proliferation. They submit on the basis of their observations that the submucosal thickening is an important factor in the formation of the pedicle of the adenoma. Perhaps of more importance, as suggested in their publication, is the possibility that the degree of submucosal reaction may be an indication of the host's capacity to react to a stimulus in the overlying mucosa and create a barrier against the abnormal mucosal proliferation.

The degree of submucosal reaction has a wide range of variation from minimal thickening, as seen in sessile polyps, to rather extensive thickening noted in pedunculated polyps. The importance of this local barrier, if it may be considered such, in terms of host resistance is the generally accepted belief that adenocarcinoma occurring as a pedunculated lesion carries a more favorable prognosis than one occurring as a sessile lesion.

Two important questions, it seems to us, are raised by the preceding hypothetical considerations. Does the development and morphologic configuration of a polyp represent a manifestation of host resistance, and if so, do patients with adenocarcinoma of the colon and rectum have a more favorable prognosis if the lesion coexists with benign adenomatous polyps? It is not to be concluded necessarily, however, that the carcinoma arose from an antecedent adenomatous polyp.

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METHOD OF STUDY

In order to examine the concept that patients who are "polyp formers" have greater resistance to malignant lesions of the bowel than "nonpolyp formers" a group of patients operated upon at University Hospitals of Cleveland during the years 1950 and 1951 for adenocarcinomas of the colon and rectum were studied. They were divided into two groups; group I, adenocarcinoma with associated polyps, and group II, adenocarcinoma without associated polyps. It must be stressed at this point that the adenocarcinomas were of the garden variety and that in the two groups they were identical with respect to their gross and histologic characteristics. Excluded from consideration as the primary adenocarcinoma from both groups are pedunculated adenomatous polyps that are diagnosed histologically as having a malignant focus with or without invasion of the pedicle.

These 2 particular years were chosen for the study because they provide a minimum of 6 years' follow-up and at the same time are years during which the technical aspects of surgery of the colon were essentially standard.

TABLE I.—SUMMARY OF DATA

	Group I Colorectal cancer with associated polyps		*Group II Colorectal cancer without associated polyps*	
	No.	*Per cent*	*No.*	*Per cent*
No. of patients	28		59	
Mean age, years	62		60.5	
Males	15	53	30	51
Females	13	47	29	49
Mean duration symptoms, weeks	35		20	
Cancer site				
Rectosigmoid	19	67	32	54
Left colon	3	11	15	26
Transverse colon	1	4	2	3
Right colon	5	18	10	17
White	25	89	53	90
Negro	3	11	6	10
Private	14	50	33	56
Staff	14	50	26	44
Positive lymph nodes	8	29	20	34
Local extension (serosa and/or pericolic fat)	11	39	30	51
Living 6 years	21	75	27	46

The following criteria were established for the selection of patients to be included in the study:

1. The patient must have undergone a "curative resection" (no evidence of distant metastases) for adenocarcinoma of the colon or rectum.

2. To be included in the polyp forming group (group I) a *histologic* diagnosis of adenomatous polyps had to be made on a specimen removed at some time during the patient's hospitalization. A few of the patients had polyps removed through a sigmoidoscope. Most of the polyps, however, were contained within the surgical specimen that had been excised for the adenocarcinoma.

3. Patients who died during the immediate postoperative course were excluded.

4. Only patients in whom a satisfactory follow-up could be obtained are included. Five patients without associated polyps could not be followed.

A total of 87 cases qualifying for the above criteria were collected from our files during the 2 year period comprising this study. There were 59 patients with adenocarcinoma of the colon or rectum in whom no polyps were demonstrated or thought to exist at the time of surgery and in whom no polyps have been found during the 6 year period of observation. A group of 28 patients with adenocarcinoma of the colon and rectum had one or more histologically proved adenomatous polyps in the colon or rectum at the time of surgery for cancer or had such a lesion removed either before or after surgery.

Inasmuch as we were interested in the question of a patient's "resistance" to his cancer rather than cure, the end point in the study is simply whether the patient is alive and not necessarily free of disease at least 6 years following operation. The latter condition would be difficult to ascertain without error in both groups.

Other data were obtained upon the two groups of patients from the hospital records to determine whether the composition of the two patient populations made valid a comparison and also in order to examine various parameters that might influence patient survival.

These data are included and summarized in Table I.

It may be seen from the accompanying table that groups I and II are comparable except for the presence or absence of polyps. Patients who are known to have had adenomatous polyps in conjunction with a frank adenocarcinoma of the bowel have a 75 per cent 6 year survival rate compared to a 46 per cent 6 year survival rate in the group without polyps (Fig. 1).

DISCUSSION

One point deserving discussion is the fact that a slightly greater percentage (12 per cent) of patients without polyps have evidence of local extension into serosa or pericolic fat. However, what may be of signal importance in this regard is that this finding itself may reflect a difference in host resistance. When local extension was present 45 per cent of the polyp formers survived while only 23 per cent of the nonpolyp forming group survived (Fig. 1). The incidence of lymph node metastases in the two groups is quite comparable; 29 per cent

of group I having positive lymph nodes, and 34 per cent of group II. Here again, however, one gets the distinct impression that the patients with polyps have greater resistance to the disease as evidenced by a 50 per cent survival in the face of lymph node metastases as compared to a 25 per cent survival for the group who did not have polyps (Fig. 1).

Another item of interest is the data in the two groups concerning the duration of symptoms. Although the group with adenomatous polyps had a significantly longer period of symptoms prior to surgery for their cancer, it is our belief that this is an area where reliable information is most difficult to obtain. To attempt to date the onset of an insidious change in bowel habits even in the case of the most intelligent, bowel-conscious observer strikes us as an almost impossible task. If true, however, the longer duration of symptoms in the polyp forming group might be interpreted to indicate host resistance.

The question can be raised, of course, that polyps which have gone unrecognized are in fact present in some patients in group II. This possibility cannot be denied but it should be pointed out that if such patients exist, they are among those of the present day survivors.

A criticism of this study unquestionably is the limited number of patients. However, the increased survival rate of patients with carcinoma who have associated polyps is so striking that it seemed worthwhile recording. If we calculate the statistical significance of the difference between the two percentages we find the observed differences between the percentage survival to be 2.53 times the standard error. Where the observed difference (29 per cent) is at least twice the standard error, in this case 11.44, it may be concluded that the difference would be quite rare by chance. P = < .05- > .01.

Certain assumptions have been made which may eventually prove to be unwarranted but at the moment are in harmony

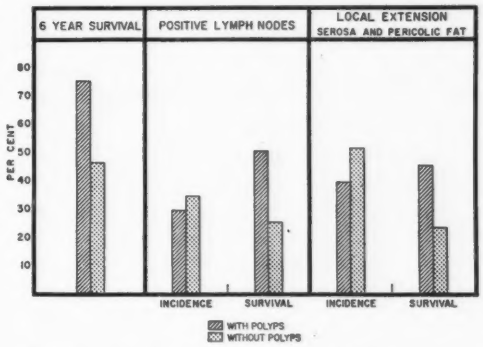

FIG. 1. Study of curative resections for adenocarcinoma of the colon and rectum in patients with and without associated adenomatous polyps.

with most present day thoughts concerning the pathogenesis of adenomas and carcinoma. We believe the cancers in both groups to be of equal "virulence." When adenomatous polyps and frank adenocarcinoma coexist we believe that there is a demonstrable relationship manifested in this study by increased survival time. A relationship is thought to exist by many clinicians and pathologists. Helwig in a study of colons in 1,460 consecutive autopsies concluded that most carcinomas probably arise from antecedent adenomas but adds that they may occasionally arise directly from the mucosa. The cases he cites to demonstrate this latter point are 2 carcinomas of the colon. The larger of these measured 11 millimeters in its greatest dimension; both had invaded the muscle of the bowel wall. Are these observations to be explained by suggesting that these very small carcinomas were extremely "virulent" or did the hosts lack resistance? Is it mere coincidence that neither case had associated polyps?

CONCLUSION

A follow-up study on two groups of patients undergoing curative resection for adenocarcinoma of the colon and rectum was undertaken. One group had associated adenomatous polyps, the other group apparently did not.

The results of the study indicate that the polyp-forming group had a 75 per cent chance of being alive 6 years after resection compared to a 46 per cent chance for patients without polyps.

Possible implications of these findings are discussed. It is recognized that a larger group of patients must be studied to confirm the hypothesis even though these data have statistical significance.

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EDITORIALS

DIFFICULTIES IN THE DIAGNOSIS OF PANCREATIC DISEASE

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THE PROBLEMS encountered in establishing a diagnosis of pancreatic disease, either acute or chronic, are clearly related to the anatomy and physiology of this organ. Situated in a relatively inaccessible retroperitoneal location, this long and slender gland may be extensively diseased without involving adjacent viscera. Lacking a lumen and having a ductal system that communicates with the intestine via two minute orifices, an opportunity to delineate its interior by means of retrojection of radiopaque material from the duodenum is impossible. Unfortunately, selective excretion of a radiopaque dye, as employed in cholecystography and urography, has never been accomplished. Localized or diffuse enlargement of the pancreas, resulting from tumor, cyst, or inflammation, may attain considerable size without being palpable to the examining fingers.

Two features of the anatomic relationships of the pancreas will occasionally provide significant diagnostic information. More important of these is the location of the distal end of the common bile duct behind or within the head of the pancreas, a relationship that accounts for common duct obstruction with resulting jaundice in neoplastic and occasionally in inflammatory lesions involving this part of the gland. Less important is the intimate relation of the body and tail of the pancreas to the splenic artery and vein, leading at times to splenomegaly on the basis of neoplastic embolization into the splenic artery or occlusion of the splenic vein.

X-ray studies may in some cases demonstrate changes indicative of acute or chronic disease of the pancreas. In acute pancreatitis an isolated loop of distended small bowel, situated in the left upper abdomen, is quite commonly observed in a plain film of the abdomen. The development of a small to moderately large pleural effusion on the left side is occasionally seen in acute disease. The demonstration of calcific radiopacities in the region of the pancreas represents unequivocal roentgenologic evidence of chronic disease. Widening of the duodenal loop and demonstration of the inverted 3 sign of Frostberg, as seen on barium meal, provide in my opinion highly undependable evidence on which to base a diagnosis.

The development of diagnostic aids based on an evaluation of the physiology or functional activity of the pancreas has been more rewarding than information related to anatomic deformity of the gland. Few of these tests, however, relate to the endocrine function of the pancreas inasmuch as far advanced disease of this combined exocrine-endocrine gland may exist without measurable disturbance of its endocrine function. While the development of diabetes mellitus or the demonstration of a diabetic glucose tolerance curve may provide some support-

ing evidence of pancreatic disease, there is little constancy to these findings.

Laboratory determinations based on measurements of the exocrine function of this gland have provided the most dependable assistance in the diagnosis of pancreatic disease. These tests are, in general, designed to measure either directly or indirectly the activity of one of the pancreatic enzymes. Direct measurement of enzyme activity may be carried out either on the duodenal aspirate or the blood serum. Determination of the enzyme and bicarbonate content of the duodenal aspirate has proved in our hands to involve too many technical difficulties and variables to be well suited to routine use. Determinations of enzyme levels in the blood serum are without doubt the most valuable and most commonly used laboratory aids. The serum amylase determination, carried out by means of one of the several acceptable methods, finds its greatest value in the diagnosis of acute pancreatitis. However, the occurrence of hyperamylasemia in a number of acute and chronic nonpancreatic diseases, as well as following the administration of various commonly used drugs, places serious limitations on its significance. In chronic pancreatic disorders a normal or subnormal serum amylase level is present about as often as an elevation, thereby eliminating the significance of a normal serum amylase in these conditions. Attempts to provoke an elevation of the serum amylase in chronic pancreatitis by using pancreatic stimulants, such as secretin, prostigmine, and pilocarpine, have been of limited value. An abnormally low serum amylase has been shown to occur with significant frequency in cancer of the pancreas and in far advanced chronic pancreatitis(1). Determination of the serum lipase level of the blood has been employed principally in the diagnosis of chronic lesions of the pancreas. In the diagnosis of acute pancreatitis this test has the serious disadvantage of being too time-consuming and in the experience of most observers is not as constantly elevated as the amylase level. In chronic pancreatic diseases I have rarely observed an elevated serum lipase without a concomitant elevation of the serum amylase.

It is not surprising that little investigation of serum trypsin has been carried out. These studies are technically difficult and only indirectly measure trypsin. Inasmuch as the blood serum always possesses an antitryptic activity, the measurement of the antitrypsin provides an indirect index of the amount of trypsin in the blood serum. Some studies(2) indicate that a reduction of the antitrypsin level, or in other words, an increased tryptic activity of the blood, occurs in acute necrotic and not in acute edematous pancreatitis. Improvement in the technical methods of trypsin-antitrypsin determination should encourage a more accurate reevaluation of this enzyme balance, and its possible usefulness in distinguishing between the lethal necrotic and the self-limited edematous form of acute pancreatitis.

Recent investigations of Houck and associates, based on the original observation of Kowlessar and McEvoy, indicate that another enzyme, desoxyribonuclease (DNAase), is specifically elevated in necrosis of the pancreas. The former investigators have reported that in experimental studies elevation of the serum amylase is provoked by ductal obstruction and not by necrosis of the pancreas, whereas the serum desoxyribonuclease is elevated as the result of necrosis and not by obstruction of the pancreatic ductal system. Clinical substantiation of these results would provide another means of distinguishing between the edematous and necrotic form of pancreatitis.

Metabolic balance studies in which the intake and output of fat, protein, and carbohydrate are determined chemically over varying periods of time have been employed to measure exocrine pancreatic function in suspected cases of chronic pancreatic insufficiency. However, these balance studies are too cumbersome for practical use and have been limited mainly to research laboratories. Even under these conditions balance studies of protein and carbohydrate have failed to

provide useful diagnostic data. Fat balance studies, on the other hand, quite accurately measure chronic pancreatic insufficiency(3).

The use of radio-isotopes has introduced another effective tool in the diagnosis of chronic pancreatic disease. The oral administration of I^{131} tagged triolein in olive oil provides a relatively easy method of obtaining a blood lipid curve that accurately reflects fat digestion and absorption. The normal blood fat curve reaches a peak at 4 to 6 hours, returning to the original level in 8 hours. In chronic pancreatic disease the level remains absolutely or relatively flat. The substitution of I^{131} tagged trioleic acid for triolein permits differentiation of the fat absorption error occurring in intestinal disease, i.e. sprue, ileitis, from that occurring in pancreatic disease. In the former trioleic acid absorption is defective while in pancreatic disease the fatty acid absorption is unaffected, as Duffy and Turner have indicated.

More recent studies in our laboratory and by Osmon and associates have shown that serum turbidity as measured by spectrophotometric methods following the oral administration of plain olive oil produces a curve identical to that obtained with I^{131} tagged triolein, thereby eliminating the need of the isotope method and providing a much simpler method that lends itself to use in the routine hospital laboratory.

In summary, a review of the current status of diagnostic methods employed in the diagnosis of pancreatic disease leads one to the inescapable conclusion that none of these laboratory aids possesses precision sufficient for a dependable diagnosis in all cases of pancreatic disease. While a diagnosis of acute pancreatitis cannot be made confidently without demonstration of an elevation of the serum amylase, hyperamylasemia should not deter one from making a diagnosis of acute nonpancreatic disease, i.e., peptic ulcer. Negative diagnostic studies are so commonly encountered in chronic pancreatic disease that clinical findings must form the sole basis for diagnosis in many cases. An awareness of this fact is essential if one is to avoid harmful delay in awaiting laboratory support of a clinical diagnosis, particularly in the case of neoplastic or chronic inflammatory disease.

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CANCER ORTHODOXY

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A GREAT DEAL of recent writing on the subject of cancer questions or challenges most of the basic assumptions upon which orthodox methods of management are based. While an unwillingness to accept dogma is a wholesome aspect of the scientific mind, the substitution of a whole new unproved concept may merely serve to confuse the picture without offering any helpful contribution.

These new heresies have many superficial points of similarity with the religious schisms which characterized the Protestant Reformation. The challenge of dogma and rebellion from authority are the common points of departure. It should be remembered, however, that the orthodoxy of cancer ideology is based not upon divine revelation but upon the accumulated observations and clinical experiences of generations of practitioners. Some of the newer promulgations, such as "biologic predeterminism," seem to parallel the doctrine of original sin. Some of the newer heretics seem to bask in a smug certainty of righteousness comparable to the state of grace so eagerly sought by some of the earlier divines.

Unfortunately, some of these newer concepts appear to be wholly sterile and to lead to no fruitful amelioration of management. To sit down with the patient and deplore the whole disease process will not cure cancer, nor even comfort the sufferer. The attitude of mind that accepts predeterminism is close to despair and decries the physician's obligation to endeavor to better the situation.

The pernicious mischief of these heresies is that they are eagerly embraced by the incompetent and ignorant as justification for deviations from approved methods of management. To destroy the physician's faith in his capacity to modify events in behalf of his patient, to deny him the belief that there is a way of salvation sanctioned by authority, is to nullify his social usefulness. Until the heretics can enunciate a formula more constructive than our present orthodoxies, only harm can result from dissemination of their ideas.

THE SURGEON AT WORK

PERFORATION OF THE COLON DURING ENEMA INTO THE COLONIC STOMA

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PERFORATION OF THE COLON by the enema tube is an ever present threat to the patient who has had a colostomy. Fortunately, such an accident is seen infrequently by any single surgeon. Though the occurrence of this often disastrous complication is probably higher than is generally realized, it is of interest that some reviews of complications following colostomy have failed to mention perforation.

Our experience with several perforations caused by enema tube stimulated us to review such cases encountered by the surgical staff of this hospital. We are reporting upon 17 patients who suffered perforation of the colon in the course of an enema into the stoma. No attempt is made to establish the true incidence of this complication since it is patently impossible to obtain significant statistical data about an event which may occur more than 20 years after the original procedure. The pertinent information concerning these 17 patients is summarized in Table I.

CASE ANALYSIS

There was an even representation of the sexes. In most patients, the stoma was the result of combined abdominoperineal resection for carcinoma. In 3 patients, the lateral gutter had not been obliterated, so it would appear that the fixation and kinking that possibly result from this maneuver were not necessarily a factor in producing this complication.

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Perforation occurred at postoperative intervals ranging widely from shortly after the initial operation to 22 years following surgery. In 7 patients, perforation occurred within 6 months of the initial operation. Three of the 17 perforations occurred during barium enema. Five enemas were administered by nurses: 3 in the hospital, 1 at home, and 1 in a nursing home. In no case was there a perforation immediately after the original operation. Perforations did occur in the hospital during subsequent admissions for other or associated problems.

All of these patients had been managed by irrigations either daily or every other day. A few of the patients experienced difficulty in inserting the enema tube or were having difficulty in the management of their stoma at the time of perforation. On the other hand, 1 patient suffered a perforation while inserting the tube and irrigating continuously in advance of its tip. This has been advised as a method of preventing trauma. In 1 patient, perforation of the colon was caused by inserting a foreign body into the stoma to break up a fecal impaction.

In 8 patients whose enema results were described following the perforating incident, 6 had no returns. In most patients pain followed immediately.

Two of the perforations occurred within the abdominal wall. Fifteen perforations were intraperitoneal. In 10 instances, the perforation was uniformly found a short distance below the peritoneum within 2½ inches of the abdominal wall. The perforation was between 4 and 6

TABLE I.—SUMMARY OF CASES

Case No.	*Age, yrs.*	*Sex*	*Original diagnosis*	*Original operation*	*Interval between original operation and perforation*	*Circumstances of perforation*	*Interval between perforation and hospital admission*	*Time of operation after admission*	*Operative findings*	*Operation performed*	*Result*
1	40	F	Ca. rectum	Abd. per. resection	1 mo.	Home; self	10 days	Immediate	Abdominal wall dissection	Drainage	Satisfactory
2	69	F	Ca. cervix, radiation stricture	Sigmoid colostomy	1 mo.	Hospital; nurse	—	Immediate	Intraperitoneal perforation	Resection	Satisfactory
3	51	F	Sigmoid fibrosis	Abd. per. resection	4 yrs.	Home; self	2 days	Immediate	Abdominal wall extravasation	Transverse colostomy	Satisfactory
4	71	M	Ca. rectum	Abd. per. resection	19 yrs.	Home; self	Same day	Immediate	Intraperitoneal perforation	Resection	Satisfactory
5	68	M	Ca. rectum	Abd. per. resection	3 yrs.	Home; self	6 days	2 days	Intraperitoneal perforation and abscess	Transverse colostomy	Satisfactory
6	73	M	Ca. rectum	Abd. per. resection	2 yrs.	Hospital; barium enema	—	Immediate	Retroperitoneal barium	Transverse colostomy	Died
7	90	F	Ca. rectum	Abd. per. resection	3 mos.	Hospital; nurse	—	Immediate	Intraperitoneal perforation	Resection	Died
8	72	F	Ca. sigmoid	Sigmoid colostomy	16 days	Home; nurse	Same day	Immediate	Intraperitoneal perforation	Transverse colostomy	Satisfactory
9	65	F	Ca. rectum	Abd. per. resection	6 mos.	Home; self	2 hrs.	Immediate	Intraperitoneal perforation	Transverse colostomy (later resection)	Unsatisfactory initially
10	71	M	Ca. rectum	Abd. per. resection	4 mos.	Home; nurse	5 hrs.	Immediate	Intraperitoneal perforation	Resection	Satisfactory
11	81	F	Diverticulitis	Transverse colostomy	5 yrs.	Hospital; barium enema	—	Immediate	Intraperitoneal barium (perf. of distal colostomy)	Suture and drainage (transverse colostomy present)	Died
12	67	M	Ca. rectum	Abd. per. resection	21 yrs.	Hospital; barium enema	—	Immediate	Intraperitoneal barium; ileum injured	Resection of injured colon and ileum	Died
13	63	F	Ca. rectum	Abd. per. resection	22 yrs.	Home; self	Same day	Immediate	Intraperitoneal perforation	Resection	Satisfactory
14	50	M	Ca. rectum	Abd. per. resection	2½ yrs.	Home; self	Same day	24 hrs.	Intraperitoneal perforation and ileal injury	Transverse colostomy; ileal resection	Died
15	71	F	Ca. rectum	Abd. per. resection	5 mos.	Home; self	7 hrs.	Immediate	Intraperitoneal perforation	Resection	Satisfactory
16	49	M	Ca. rectum	Abd. per. resection	3 yrs.	Home; self	2 hrs.	Immediate	Intraperitoneal perforation	Resection	Satisfactory
17	81	M	Ca. rectum	Abd. per. resection	7 yrs.	Home; self (used stick to disimpact)	?Same day	Immediate	Intraperitoneal perforation	Resection	Satisfactory

inches from the abdominal wall in 3 cases and "in the lateral gutter" in 1 case. With the exception of 1 patient who presented himself at the hospital 6 days after perforation, the greatest delay prior to admission was 7 hours.

With 2 exceptions, immediate surgery was performed. The patient who presented himself 6 days after perforation was not operated upon until 48 hours after entry. Another patient who was deemed too ill for immediate surgery was operated on after a 24 hour attempt to improve his general physical condition. Resection of the perforated segment with construction of a new stoma was done in 10 patients. The remaining patients had a proximal defunctioning transverse colostomy with suture of the perforation whenever possible. In all instances, the site of perforation was drained. Incision and drainage were done in 2 patients in whom perforation was within the abdominal wall. One of these patients had had a prior transverse colostomy.

There were 5 deaths, all caused by intraperitoneal perforation. Three of these 5 deaths were the result of perforation during barium enema with escape of barium into the peritoneal cavity. One of these 3 patients may have had an immediately prior perforation due to a preparatory enema. This patient was 81 years of age and confined for mental illness, so it was not possible to be sure whether the perforation occurred during the preparation or during the subsequent barium enema. Death occurred in the patient whose operation had been delayed 24 hours because of poor physical condition. He failed to improve significantly during this period of preparation and underwent surgery at the end of that time. One patient succumbed who was operated on immediately and who did not receive a barium enema. This patient was 90 years old and debilitated.

When the fatalities are grouped by procedure, it is found that 2 deaths occurred after resection and new colostomy. One patient had a barium enema and the other was 90 years old. The remaining 3 fatalities occurred when transverse colostomy alone was done. Two patients had barium enemas and 1 patient was operated on after a 24 hour delay. Three patients survived after simple transverse colostomy and drainage. In the patient admitted 6 days after perforation with a localized abscess, this procedure was elected as the simplest and most effective. In another patient with irresectable, widespread carcinoma of the rectosigmoid who had had a palliative sigmoid colostomy, proximal colostomy was elected as the minimal procedure. In a third patient, proximal colostomy proved unsatisfactory because of repeated episodes of drainage from the original site of perforation. Ultimately, resection of this segment with establishment of a new end stoma was necessary.

PREVIOUS REPORTS

Gabriel (4, 5), reported his experience with 9 cases of perforation after colostomy during a 7 year period. One of these occurred in the hospital, others within 3 years after operation. The perforations were usually within 2½ inches of the stoma, into the abdominal wall, intraperitoneally or retroperitoneally depending upon location of the perforation. In 3 patients, no surgery was done; in 2 the distal perforated bowel was resected; in 3, a transverse colostomy was done with drainage; all 8 patients died. One with extraperitoneal perforation survived. These disasters confirmed his opinion that washouts should be abandoned in stoma care.

An early report from the Massachusetts General Hospital (2) demonstrated that perforation could occur even after many years of experience with administration of enemas. Silvers reported a perforation occurring 5 years postoperatively and advised the use of a soft catheter and avoidance of force in introducing the enema tube. The method of running the catheter tip a short way through a nipple which occludes the stoma in order to eliminate the danger of perforation has been emphasized by Davis. Additional instances of perforation have been reported by numerous authors. Zheutlin records 12 perforations in the course of barium enema and Berk added another.

Hoffman and Macht added 2 successful cases, 1 patient having been treated by suture and drainage and the other by transverse colostomy, and they recommended the use of a Foley catheter to prevent traumatic perforation. Klein and Scarborough reported experience with 12 cases of perforation of the colon during stoma irrigation. One-half of the perforations occurred in the hospital, the others during a 10 year period. Seven patients were treated conservatively with spontaneous drainage in 3. Two perforations were closed. Two patients had transverse colostomies and in 1 patient drainage was accomplished without colostomy. In no

instance was the bowel mobilized and a new colostomy done; all patients recovered.

COMMENT

There is nothing occult about this syndrome in either etiology or symptoms. The history in brief is that of an enema administered sometimes with difficulty, usually with no returns followed by immediate pain. The patient then becomes progressively ill and passes into a state of collapse. The findings are those of visceral perforation with early onset of a toxic state. Diagnosis is generally obvious. This small group of cases certainly suggests, as has been well recognized, that perforation during barium enema is usually lethal. Perforation into the abdominal wall leads to septic complications, but in itself is not lethal. The 1 death following delay of surgery and the survivals following immediate surgery suggest that defunctioning and relief of contamination are urgently indicated. Operation should not be delayed long in an effort to improve the patient's condition. There was 1 instance of prolonged delay in admission to the hospital, but this patient had a well localized abscess.

Although the number of cases is not great, the results in our series seem to demonstrate that, in general survival may be expected with either resection and another colostomy or diversion by simple proximal transverse colostomy and drainage of the site of perforation. We, therefore, favor the definitive procedure of resection of the perforation with construction of a new stoma whenever this can be done. Several of these patients were old and in poor general physical condition but tolerated this simple operation well without postoperative difficulties. On the other hand, when the patient is in very poor condition or when the original colostomy was palliative without hope for long term survival, it appears justifiable to perform simple transverse colostomy and drainage. In 1 patient, simple transverse colostomy proved functionally unsatisfactory and required later resection. This fact has strengthened our opinion that whenever possible primary resection should be the procedure of choice.

While the course of therapy seems relatively clear, there is no simple answer to the problem of prevention unless we accept the conclusion reached by Gabriel that the washout system be abandoned entirely. Both patient and physician, however, are loath to abandon the predictable functioning of a stoma managed by irrigation.

CONCLUSIONS AND SUMMARY

1. Seventeen patients who suffered perforation following a colostomy are reported.

2. There were 5 deaths. Three patients received barium intraperitoneally, 1 was operated on after a delay of 24 hours, and 1 was debilitated and over 90 years old.

3. The treatment of choice is excision of the perforated segment with fashioning of a new stoma. Simple proximal transverse colostomy and drainage of the perforation may suffice in the critically ill.

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INGUINAL HERNIA IN FEMALE INFANTS AND CHILDREN

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DURING THE COURSE of an inguinal hernia repair in a 6 year old girl, a normal fallopian tube and ovary were sacrificed. Upon hearing about this catastrophe, we were prompted to review the management of inguinal hernia in female infants and children. The surgical literature is replete with articles concerning the management of inguinal hernia in male infants and children, but little attention is focussed upon this condition as it appears in the female. In fact, a review of the literature discloses only 2 articles, those of Arnheim and of Pender and their associates, specifically devoted to this subject. Pender and his associates report the sacrifice of the internal genitalia in 6 per cent of all cases. We would like to narrate our experience with 57 patients and consider the optimum surgical care of this condition. In our opinion, the internal genitalia should never, or rarely ever, be sacrificed.

EMBRYOLOGY

The embryologic basis for indirect inguinal hernia in females is not clearly defined. Much of the confusion centers about the canals of Nuck. The labia majora are derived from the genital swellings and are homologous with the male scrotum. In the female these folds become heavily infiltrated with fat but do not normally contain any cavities within them comparable to the scrotal pouches. In rare instances, there are rudimentary tongues of peritoneum extending for variable distances into the labia, and these anomalies have been termed the canals of Nuck.

Clinically, the indirect inguinal hernia sac is intimately adherent to and frequently cannot be detached from the round ligament of the uterus. It would seem more reasonable to associate a potential indirect inguinal hernia with the development of the round ligament. By the beginning of the third month of fetal life a continuous cord of dense mesenchyma extends from the region of the uterus to the labium majus. This cord soon becomes fibromuscular and persists as the round ligament of the uterus. Where the round ligament passes through the abdominal wall (inguinal ring), muscles organize around it and produce the slanting, tubular, inguinal canal. During this course of events it would be possible for a process of peritoneum to be carried along constituting a potential hernia. If this bay of peritoneum fails to close off entirely and disappear, an inguinal hernia would result.

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DIAGNOSIS

The commonest presenting complaint in our experience is a recurring inguinal mass of varying size. Associated pain would seem to be infrequent as evidenced by a 6 year old girl who viewed the reappearance of a right inguinal mass with little concern and the remark, "look Mommy, there's that funny bump back again." Only 1 patient in this group had right lower quadrant abdominal pain at the time of admission, which proved to be due to an incarcerated right indirect inguinal hernia. A history of recurring swelling in the inguinal region or labia is the most decisive factor in arriving at a diagnosis of inguinal hernia.

Physical examination may reveal a palpable mass if the hernial sac contains a loop of small bowel or internal genitalia. The majority of inguinal hernial sacs in female infants or children are empty. In an infant, the short omentum cannot reach as far as the internal ring which is often a very small opening. The most frequent finding at physical examination is the hernial sac itself and gentle palpation with the index finger lying along the course of the inguinal canal will detect a "silky," slippery sensation. This finding results from sliding the walls of the hernial sac against one another. If the patient's intra-abdominal pressure is raised by crying or straining, an obvious bulge may appear. It is important to examine both inguinal regions carefully as bilateral inguinal hernias occur quite frequently. In this group of patients there were 8 instances of bilateral inguinal hernias.

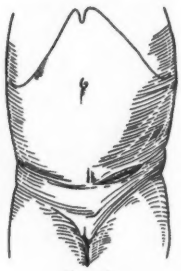


FIG. 1.

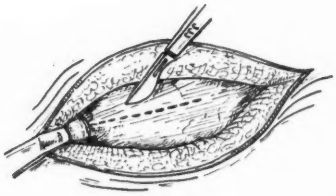


FIG. 2.

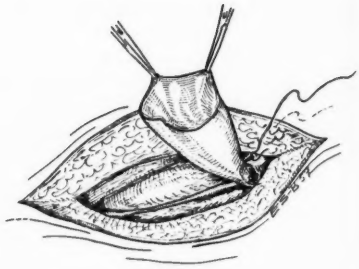


FIG. 3.

FIG. 1. The incision is made in the transverse skin crease.

FIG. 2. The wound is deepened through subcutaneous tissue and Scarpa's fascia to the aponeurosis of the external oblique which is split in the direction of its fibers, including the external inguinal ring as indicated by the dotted line.

FIG. 3. The hernial sac is freed up to its origin at the internal ring and, if empty, the sac is closed with a high purse-string suture.

THE DIFFERENTIAL DIAGNOSIS

The differential diagnosis of inguinal hernia in a female infant or child should include consideration of a hydrocele of the canal of Nuck and inguinal adenitis. Femoral hernia is a rare finding in children, in a series of 1,000 hernia operations in patients up to age 12 years old, there was a total of 4 femoral hernias, of which 3 were in females. Inguinal hernia is easily differentiated from a femoral hernia which is entirely external to the spine of the os pubis and the inguinal canal is empty. In an adult, hydrocele of the canal of Nuck is felt as a small, tense, fluctuating tumor which cannot be forced out of the inguinal canal. Preoperative diagnosis of hydrocele of the canal of Nuck is uncommon, and there were no such lesions in this group. Inflamed inguinal lymph nodes may result from staphylococcal or streptococcal infection of the perineum, anus, or lower extremity. Differential diagnosis in this instance should present no problem and inguinal lymphadenitis is mentioned here only for the sake of completeness.

AGE OF REPAIR

Potts and others have emphasized the high incidence of incarceration in infants under the age of 6 months; the 3 patients in the present group admitted with incarceration were 2 months, 2 months, and 7 weeks of age, respectively. Psychologic studies in various centers throughout the country tend to indicate that separation of the mother and child between the ages of 1 and 3 years is the most undesirable period from an emotional point of view. Since an occasional indirect inguinal hernia in a female infant will heal spontaneously during the first year of life, it is our policy to perform surgery in those under 1 year of age only for troublesome hernias or for those with a tendency to incarceration. Since the average patient stays in the hospital 3 or 4 days only, often in the same room with the mother, we do not hesitate to carry out elective surgical repair of the hernia after the patient's first birthday. Upper respiratory infection or recent exposure to contagion constitutes a definite contraindication to general anesthesia which is the anesthetic modality of choice and was employed in every instance in this group of patients.

In a child who has attained the age of reason, a simple and truthful explanation of what may be expected will pay very real dividends. A visit to the hospital, and talking with other children who have undergone similar surgery is very much worth while.

PREOPERATIVE CONSIDERATIONS

Following admission, a complete blood count and urinalysis are obtained. Ordinarily no skin shaving or preparation is necessary. No other preanesthetic measures are employed save withholding oral intake for 6 hours in an infant and 8 hours in an older child. There is no need or indication for a preoperative enema. We do not routinely employ preanesthetic medication, and in an infant no medication is given since our anesthesiologists prefer to use orotracheal suction once or twice, to control secretions, during the course of the operation which is conducted under open, drop ether anesthesia. In older children

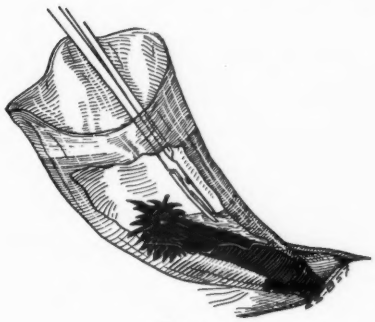


FIG. 4.

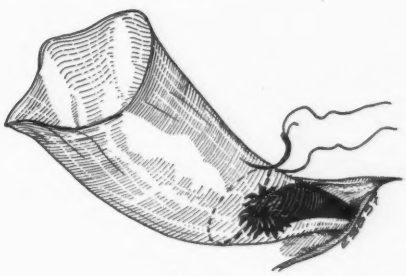


FIG. 5.

FIG. 4. When the fallopian tube is adherent within the sac by a thin avascular adhesion this is divided, the contents are reduced, and the sac is ligated high.

FIG. 5. If the fallopian tube comprises one wall of the hernial sac, the purse-string suture is placed low, distal to the point of attachment, or if need be a LaRoque procedure is carried out.

who understand what is being done and who are co-operative, we believe that a few unpleasant seconds during induction of anesthesia is preferred to administering general anesthesia to a patient rendered almost comatose by preanesthetic sedation. We do not hesitate, however, to use oral barbiturates or avertin in older, apprehensive, or less co-operative children.

SURGICAL MANAGEMENT

Figures 1 through 8 detail the steps of the operation. With the patient under satisfactory general anesthesia, the skin of the abdomen, groin, and upper thigh is prepared with an antiseptic solution and the operative field appropriately draped with sterile linen. While the classical oblique inguinal hernia incision affords excellent exposure, a short transverse incision in the skin crease above and parallel to Poupart's ligament will give a far more satisfactory cosmetic result. This incision is deepened through subcutaneous fat to Scarpa's fascia which is always a very well defined layer in infants and children. Hemostasis is maintained with ligatures of No. 4-0 plain catgut. The external oblique aponeurosis is split in the direction of its fibers down to and including division of the external inguinal ring. The inguinal canal is thus exposed and the hernial sac mobilized. Often the hernial sac cannot be separated from the round ligament and, if need be, there should be no hesitation in dividing this structure. Once the hernial sac has been freed up to its neck it is opened and the contents inspected.

In the majority of cases the hernial sac is empty and here a high suture ligation with No. 3-0 or No. 4-0 black silk completes this portion of the procedure. In our group of 57 children, the fallopian tube or ovary was present within the hernial sac in 7 instances. If the internal genitalia have simply prolapsed into the sac without being adherent to the sac wall, these structures are gently pushed back within the peritoneal cavity, and the hernial sac is closed. If the tube or ovary is adherent to the sac only by a filmy avascular adhesion, this may be divided and the structures reduced. If, however, the fallopian tube is firmly adherent as in a sliding hernia, it is dangerous to incise along the line of adherence between the fallopian tube and hernial sac as one may well damage the blood supply to the tube and ovary. It has been our practice carefully to place a purse-string suture of nonabsorbable material immediately distal to the point of attachment of the fallopian tube and close the sac at this point.

In females, there is no necessity to maintain patency of the inguinal canal so a tight, complete closure of the musculofascial wall, coupled with a comparatively low ligation of the hernial sac, produces an adequate repair. In utilizing this device no risk of damaging the infundibulopelvic ligament is taken. While we have never experienced such a situation it is conceivable that one might encounter a sliding hernia of the fallopian tube and ovary which could not be treated in the fashion just outlined. In such a circumstance, we would have carried out a LaRoque operation reducing the fallopian tube and ovary from above, through a separate incision, and then tightly closing the internal inguinal ring.

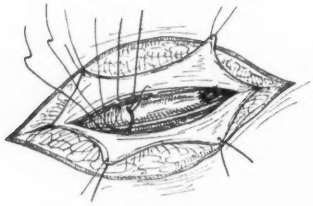
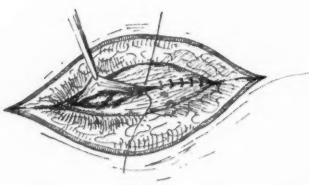


FIG. 6.



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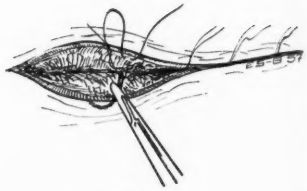

FIG. 8.

FIG. 6. The internal oblique and transverse abdominal muscles are sutured to the inner border of Poupart's ligament.

FIG. 7. Aponeurosis of external oblique is closed with interrupted sutures of fine chromic catgut.

FIG. 8. Skin edges are approximated by means of deep subcuticular sutures of No. 6-0 white silk.

The lower edge of the transversus abdominis and internal oblique muscles is sutured to the inside of Poupart's ligament, extreme care being taken not to damage or include in the suture the inguinal, hypogastric, or genital branches of the ilioinguinal, iliohypogastric, or genitocrural nerves. Damage to these nerves can cause considerable postoperative pain and atrophy to the muscles they supply, so each nerve should be isolated, identified, and preserved. The closure of the inguinal canal is carried down snugly to the pubic symphysis. The aponeurosis of the external oblique is then carefully reapproximated with very fine chromic catgut, similar interrupted sutures of plain catgut being employed to close Scarpa's fascia. The skin edges are approximated with interrupted subcuticular sutures of No. 6-0 white silk placed in the deeper part of the corium and 7 to 8 millimeters back from the incision edges as advocated by Gross. Thick collodion is applied to the incision and the operation completed.

POSTOPERATIVE CARE

With female infants and children, we have not found the Stiles dressing necessary and the postoperative care rarely presents any complicated features. Analgesics are given if required for the first 24 hours, and we allow these patients to go home 48 to 72 hours after operation. In a case of bilateral inguinal hernia repair, the patient usually stays in the hospital for 5 or 6 days. Full activity is permitted at the end of 2 weeks.

RESULTS

During the period from 1947 to 1957, 57 female infants and children with inguinal hernia have been operated upon from the ward and private services of St. Luke's Hospital in the city of New York. The operative surgery was performed by various members of the resident and attending staffs, and there have been no deaths or serious complications in this group. While follow-up examinations are incomplete, we do not know of any instances of recurrence. Four of the patients were colored, the oldest of the patients was 13 years and the youngest 54 days, with an average age of 5.6 years.

SUMMARY

In summary, we have considered the problem of inguinal hernia in 57 female infants and children. Six hernias were bilateral, 7 contained internal genitalia, and 3 were incarcerated. The embryology, diagnosis, and differential diagnosis have been briefly reviewed.

The steps in the operative procedure have been related in detail and a method of management of a "sliding hernia" of the fallopian tube or ovary has been suggested.

Sacrifice of the fallopian tube or ovary in an infant or child is a preventable catastrophe, and it is our hope that by this article we have indicated how to avoid this and other hazards in the management of inguinal hernia in female infants and children.

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A MORE RADICAL PERINEAL PHASE FOR ABDOMINO-PERINEAL RESECTION OF RECTUM FOR CARCINOMA

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> Local recurrence is an indictment of any operation and is synonymous with inadequate excision.—WANGENSTEEN and TOON.

IN 1908, Miles (3) described the combined abdominoperineal method for excision of the rectum for malignant tumors. The recognition of the importance of the lymphatics in the spread of cancer of the rectum led to his formulation of the concept of this operation, designed to remove the 3 zones of lymphatic spread: (1) upward, (2) lateral, and (3) downward. This operation became, and has remained, the basic operation for the treatment of cancer of the rectum, especially of the lower rectum. During the course of years, the operation has become modified in the direction of greater radicalism in removing the upward and lateral zones. For removal of the levator ani muscle (which Miles considered part of the lateral zone) and the zone of downward spread, however, modern surgical practice seems to have declined from the more rigid criteria of Miles. One often has the impression that the aim of the surgeon is to complete the removal of the rectum as soon as possible, rather than to continue the performance of a meticulous, painstaking radical cancer operation.

According to Miles, the excision should embrace as wide an area of skin as possible, as much as possible of the ischiorectal fat, the coccyx, the levator fascia attached to the ventral aspect of the lowermost piece of sacrum, the coccygeal muscles, and the levatores at their origin from the lateral walls of the pelvis. With few exceptions, most surgeons now perform less radical operations at this stage. As done in most hospitals today, the incision circumscribes the anus, the ischiorectal fat is removed in rather scanty fashion, the coccyx and coccygeal muscles are not removed, and the levatores are clamped and divided wherever convenient. Upon close inspection a good deal of muscle and fat are often found still attached to the pelvic walls.

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The importance of local recurrence following excision of the rectum has been repeatedly emphasized. Gilchrist and David in 1938 pointed out the high incidence of local recurrence following resections of lesions below the peritoneal reflection (30 per cent) as compared to those above (3.6 per cent). Coller and associates found that in lesions of the lowest inch of the rectum, 36.8 per cent showed evidence of node involvement up to the margins of excision of the levator ani muscle. They stated, "In untreated cases and those which have recurrences, it is not uncommon to find carcinomatous nodules in the perineum, recto-vaginal septum and ischio-rectal fossa. Consequently, operative removal should include wide excision of the peri-anal skin, ischiorectal adipose tissue and levator ani muscles." Miles (4) stated that the levators are exceedingly prone to invasion by cancer cells, and also mentioned 31 cases of recurrence in the ischiorectal fat. In reviewing cases in which the rectum had been resected for carcinoma at different levels but the sphincter had been preserved, Wangensteen and Toon found the following incidence of local recurrence for the different levels of tumor: 0 to 5 centimeters, 30 per cent; 6 to 8 centimeters, 25 per cent; 9 to 13 centimeters, 6.3 per cent; 14 to 20 centimeters, 0 per cent. Oppolzer and Nietsche in 1942 reported an even higher incidence of local recurrence: 1 to 5 centimeters, 63 per cent; 5 to 10 centimeters, 32.8 per cent; 10 to 15 centimeters, 31.6 per cent; 15 to 20 centimeters, 14.2 per cent.

Some investigators, unable to find metastases in microscopic sections of the levator ani in operative specimens, doubt its importance as a site of spread. However, Miles (4) says: "It is a very difficult matter to detect such isolated cancer cells even when a large number of serial microscopic sections have been made, but their presence has been revealed often enough to establish the fact beyond doubt that these structures are liable to be invaded during the process of dissemination." One may logically assume that, if lymphatic pathways from the rectum

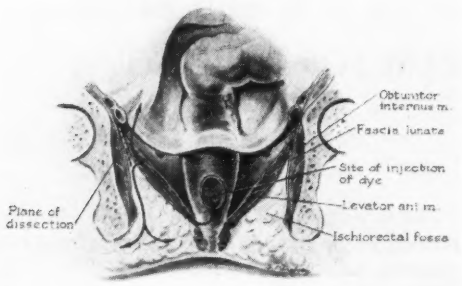

FIG. 1. Diagram of cornal section of pelvis indicating routes of spread of dye from site of mucosal injection in rectum. The broken line indicates the plane of dissection during surgery, the levator being detached from the pelvic ischiorectal fossa.

exist, the possibility of recurrence must also exist.

Lymphatic connections between the rectum and levator ani muscles and the ischiorectal tissues have been described previously, but the exact routes are not clear. A study of these lymphatics was carried out in order to map them more clearly.

METHOD OF STUDY

Direct sky blue was the dye chosen for these experiments because of its low diffusibility, its easy visibility, and because it has been extensively studied in relation to lymphatic anatomy and physiology. In each of 12 patients prepared for abdominoperineal resection of the rectum, approximately 2 cubic centimeters of the dye were injected under the mucosa of the rectum, through an anoscope, 12 to 15 hours before surgery. The site of the injection was between ¾ to 1½ inches above the dentate line, on the anterior or on the posterior aspect of the rectum, or divided between the sites. Usually the site of the injection was just below or opposite the carcinomatous lesion. Hyaluronidase was not used. By trial and error injections in other patients, it was determined that the amount of dye injected and the time interval between injection and operation were optimum. A shorter period of time did not permit the dye to travel sufficiently widely, and a longer interval tended to vitiate results by absorption into the blood stream and generalized staining. Within this time limit, however, there was much individual variation.

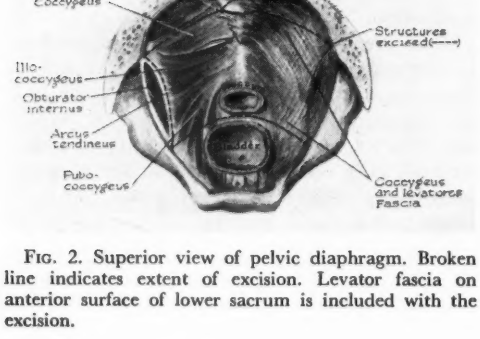

FIG. 2. Superior view of pelvic diaphragm. Broken line indicates extent of excision. Levator fascia on anterior surface of lower sacrum is included with the excision.

The results are as follows: The levatores and coccygeal muscles in all 12 cases were strongly stained with the dye, in 8 cases up to their origins from the pelvic wall and from the anterior surface of the coccyx and lower sacrum. The ischiorectal fat was less strongly stained in 7 cases, the deepest intensity of staining occurring superolaterally in the ischiorectal fossa, especially in the angle between the levator ani and the lateral pelvic wall (Fig. 1). In no instance did the dye reach the transverse perineal muscles, and, although it approached the skin closely, staining of the skin itself did not occur. In the abdomen, the dye stained the lateral pelvic and hypogastric nodes and the superior hemorrhoidal and inferior mesenteric nodes. The paraaortic nodes were stained up to the level of the lower border of the pancreas, beyond which they were not traced.

The dye apparently penetrates the rectal wall and spreads circumferentially. Then it moves downward to the levator ani muscle, whence it spreads centrifugally throughout the pelvic diaphragm, staining the supralevator and infralevator fasciae up to their origins from the arcus tendineus, from the ischial spine, and from the ventral surfaces of the coccyx and lower sacrum. Here some of the dye is gathered into lymphatic trunks and moves upward, mostly via the hypogastric and presacral nodes. However, a proportion of the dye passes into the superolateral aspect of the ischiorectal fossa whence it passes centrifugally, mostly toward the lesser sciatic notch, and, to a lesser extent, toward the skin and inguinal region.

The fascia on the ventral surface of the coccyx

and lower sacrum is the vestige of the sacrococcygeal muscle as described in the tailed monkey. This, together with the coccygeal, ileococcygeal, and pubococcygeal muscles, constitute the flexor muscles of the tail adapted, in the posturally erect apes and in man, to the function of closure of the pelvic outlet (Fig. 2). These stain as a unit, the lymphatics consisting of an extensive "lake" of fine lymphatic channels.

On the basis of these studies, I believe that in order to achieve a satisfactory perineal excision the following tissues should be removed: (1) an extensive area of perianal skin in order to approach the ischiorectal fat more widely as well as to remove the intrinsic lymphatics (the width of the excised skin should extend from one ischial tuberosity to the other); (2) all accessible ischiorectal fat posterior to the urogenital triangle, especially in the superolateral aspects of the ischiorectal fossa; (3) the levator ani muscles posterior to the urogenital triangle, including the coccygeal muscles; (4) the coccyx in order to remove the coccygeal muscles and the ventrally placed fascia.

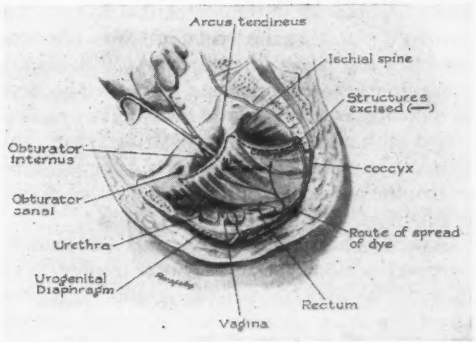

FIG. 3. Sagittal section of pelvis. Arrows indicate extent of spread of dye. The levator fascia which extends onto the anterior surface of the lower sacral segment stains strongly and is removed by the operation together with the coccyx. The scissors, separating the arcus tendineus from the lateral wall of the pelvis, indicate the plane of dissection.

TECHNIQUE OF OPERATION

During the abdominal phase of the operation, a step may be added to facilitate the perineal phase. This may be accomplished by detaching the levator from the lateral pelvic wall after the pelvic dissection has been completed. The avascular fascia between the arcus tendineus and the lateral pelvic wall is incised by scalpel and scissors, and a finger passed through this opening enters the ischiorectal fossa and may be used to dissect the fat from the lateral wall of the pelvis. Occasionally, the fascia lunata, which roofs the ischiorectal fossa (Fig. 1), may be so thick as to require incision in order to open into the ischiorectal fossa. One must remember that the direction of the finger entering the ischiorectal fossa must be toward the feet of the patient, that is, perpendicular to the vertical plane of the pelvic diaphragm of the supine patient. If the finger is directed dorsally, that is, toward the surface of the operating table, it will impinge upon the impassable sacrotuberous ligament. The separation of the levatores is surprisingly easy and bloodless, taking less than 1 minute for both sides. Infrequently, there is a wide separation between the arcus tendineus and the lateral pelvic wall. Schwalbe (6) has described hernias as having occurred through this hiatus. Detaching the levatores as an early part of the dissection is in line with one principle of cancer surgery, i.e., to make the line of excision of tissues as far removed from the tumor, and as early, as possible.

In the capacious pelvis of the female, the levator and arcus tendineus may be visualized easily. The narrowness of the male pelvis makes visualization more difficult, and the placement of deep retractors may be required.

Upon completion of the abdominal phase of the operation including the reconstruction of the peritoneal floor, construction of the colos-

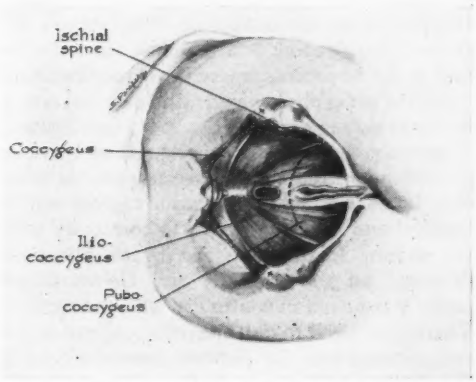

FIG. 4. Diagram of inferior view of pelvic diaphragm superimposed upon the operative view of perineum. The broken line indicates the extent of excision. *x*, Site of ligation of inferior hemorrhoidal vessels.

tomy, and closure of the abdominal wound, the patient is placed in the left lateral Sims position, the right hip being tilted forward 30 to 45 degrees. The lithotomy position is not used because of difficulty of access to the coccyx. The anus is closed with a heavy silk purse-string suture, the buttocks are drawn apart with adhesive tape straps; the perineum, buttocks, and sacral region are painted with antiseptic and draped.

A racket-shaped incision is made. The straight portion lies along the right border of the coccyx in order to avoid a painful midline scar; the circular portion encircles the anus and encloses the skin between the ischial tuberosities. By subcutaneous dissection, the coccyx is exposed and the gluteus maximus muscles are dissected off their origins from the coccyx. By moving the tip of the coccyx back and forth, the sacrococcygeal joint is located. A transverse incision is made through the posterior and lateral ligaments. By angling the knife upward or by using a periosteal elevator, the anterior ligament and as much as possible of the fascia on the anterior surface of the lower sacrum are removed. From the right side of the sacrococcygeal joint, the right coccygeal muscle is split down to the right ischial spine. This procedure is repeated on the left side. The pelvic diaphragm is now opened from behind like a trap door, with the coccyx as a handle. The levator is detached from the lateral pelvic wall from behind forward. The main blood supply, the inferior hemorrhoidal vessels, is secured by grasping the tissues just lateral to the ischial spine with a Kocher hemostat, then by suture-ligating these tissues. This procedure is repeated on the other side. This greatly decreases the bleeding which might otherwise be met as the dissection proceeds. As the dissection nears the urogenital triangle, the perineal artery on each side is divided, clamped, and ligated. Anteriorly, the dissection is deepened between the sphincter and the transverse perineal muscles. In the female, the posterior vaginal wall is exposed and may be resected in continuity with the rectum. In the male, the levator fibers are dissected off the prostate, and Denonvilliers' fascia is removed in continuity with the rectum. There is no need to pull the proximal end of the rectal stump into the perineal wound to aid in the dissection. Doing so, in fact, distorts the tissues, interfering with the dissection.

The key to dissection in this area is good retraction and exposure. There should be an abundant supply of retractors of varying types and sizes. Without these, the surgeon works under a severe handicap.

Hemostasis is no problem during this portion of the operation. The middle sacral vessels are ligated at the level of the sacral promontory during the course of the pelvic dissection. The inferior hemorrhoidal vessels, which usually appear as a sheaf of vessels proximal to the ischial spine, are clamped and ligated lateral to the spine. The superficial perineal branches encountered anteriorly are clamped and ligated when cut during the dissection. Usually, 4 ligatures in the perineum are sufficient to control the main bleeding. Troublesome bleeding from the vaginal or prostatic plexus of veins may occur, but usually the ooze is easily controlled by pressure.

When extirpation of the rectum has been completed, one may consider the possibility of loose cancer cells implanted on the raw surfaces of the pelvic and perineal tissues. In order to remove or to kill any loose cancer cells, one may irrigate with sterile water or with hydrogen peroxide solution, 1/500 bichloride solution and saline in succession, as advocated by Miles, or paint the interior of the pelvis with mild tincture of iodine, or use any of a number of carcinocidal chemicals.

Packing the pelvis is not performed unless: (1) the peritoneal floor has not been securely closed, or (2) oozing of blood has not been controlled. If the wound is not packed, the perineal wound can be closed around 2 or 3 long soft rubber drains which can be removed in 5 to 8 days. If the wound is packed to control the oozing of blood, removal of the packing can begin by the first or second postoperative day and be completed by the fourth or fifth day. Keeping the packing in for a long period of time tends to create a large fibrotic walled cavity which may take many months to fill in completely. If the wound is packed because the peritoneal floor could not be closed, the packing may not be disturbed for 2 weeks, then gradually be removed over a period of 2 to 4 days.

This technique was used in 25 patients. Healing of the perineal wound required approximately the same length of time as following the usually performed technique. There was no undue tenderness of the perineal wound in any case. In the described technique, the end of the sacrum is covered with a thick layer of fat, and

the scar is eccentrically placed. As to the effect on local recurrence, the final conclusion must await long term follow-up.

SUMMARY

1. Vital dye injection studies have demonstrated the extensive lymphatic connections between the lower rectum and the pelvic diaphragm and ischiorectal fat. While these facts are not new, they serve to re-emphasize the need for a meticulous and radical perineal phase of the combined abdominoperineal resection of the rectum, as a means of decreasing the high incidence of local recurrence associated with resection of the low-lying rectal carcinoma.

2. A technique for the performance of this part of the operation is described. It consists of removal of the coccyx and coccygeal muscles, detachment of the levator ani muscles along the avascular plane between the arcus tendineus and the lateral pelvic wall, and wide removal of the ischiorectal fat, especially in the upper lateral portions of the ischiorectal fossae.

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THE SURGEON'S LIBRARY

Reviews of New Books

TODAY, the increased interest in radiation has created a need for a general work on the effects of radiation on living systems. The extensive publicity has made the lay public x-ray conscious. Physicians in particular have been placed in the front of the controversy over radiation hazards. This new environmental danger certainly should be clarified to the inquiring public both as groups and individuals.

To the physician and other biologists, the text *Medical Radiation Biology*[1] fills that gap of knowledge. The general outline is a systemic presentation of changes in individual tissues following various forms of radiation. Other sections in this book cover phases of radiation, such as sickness, effects on neoplasms, effects of internal radiation sources, and genetic influences.

The author gives the reader a comprehensive picture, covering the historical facts and then developing well established effects and changes in tissues and in organs following a very wide variety of radiation sources.

To the reviewer, the most valuable section is entitled "Fundamental Radiation Biology." In a short 100 pages, the author clearly presents the various hypotheses explaining the mechanism of radiation effects at the cellular level. The concepts are given in a critical, nondogmatic fashion. Probably this section more than all others helps explain the basis for disagreement, now being publicly aired concerning biologic radiation effects.

The volume has an extensive bibliography of some 4,600 references.

The major fault appears in the section "Biology of Ionizing Radiations." The sharp repetitious presentation of histopathology, functional changes, chemical changes, and radiosensitivity for each tissue results in monotony. This error is partially counteracted by the ease of location for any given section.

The cost of the book may possibly be too high. Generally, the volume may be readily recommended to all workers in biologic fields. Physicians who constantly expose their patients and themselves to radiation will gain much insight into the sphere of radiation biology. As a reference work, the text will be invaluable to those working in the field.

—*M. C. Wheelock.*

[1]MEDICAL RADIATION BIOLOGY. By Friedrich Ellinger, M.D. 945 pages, illustrated. $20.00. Springfield, Ill.: Charles C Thomas, 1957.

THE AUTHOR of *Modern Perinatal Care*[2] intended it to be a practical guide to current obstetric management for general practitioners. Among the problems discussed are: abortion, pelvic mensuration, toxemias and the anemias of pregnancy, the fourth stage of labor, and the complications of pregnancy arising from heart disease, diabetes, thyroid disorders, and tuberculosis. Discussions of each are brief, but extensive bibliographies at the end of each chapter provide further source material as needed.

The suggestions given for management of these problems represent good conservative obstetrics. The chapter on nutrition and pregnancy is not as well written as the others. It includes the suggestion that calcium and phosphorus supplements be given, whereas current usage calls for nonphosphorus forms of calcium so the calcium ions are in a utilizable form. The chapters on evolution of obstetrics, legal aspects of obstetrics, and the ethics of the Catholic Church as they pertain to obstetrics are especially interesting and useful to specialists and general practitioners alike. This book is concise, easy to read, and for the most part "up-to-date." —*Charlotte Herman Kerr.*

VOLUME II of the *Textbook of British Surgery*[3] consists of a series of chapters written by different authors and, naturally, one must expect to find the material of varying quality and conciseness. This was true of volume I which was concerned with principles of surgery and surgery of the abdominal viscera.

The subjects considered are the central nervous system; the eye; ear, nose, and throat; diseases of the salivary glands, lips, tongue, cancer of the oral cavity, tumors of the jaw; the thyroid and neck in children; neck, cancer in the cervical lymph nodes, other tumors of the neck, acute infections, cut throat; diseases of the breast; thoracic wall, pleura, lung, and bronchus mediastinum; surgery of the thymus in relation to myasthenia gravis; the surgery of pulmonary tuberculosis; the surgery of the heart and the great vessels;

[2]MODERN PERINATAL CARE. By Leslie V. Dill, M.D., F.A.C.S. 309 pages. New York: Appleton-Century-Crofts, Inc., 1957.

[3]TEXTBOOK OF BRITISH SURGERY. Edited by Sir Henry Souttar, C.B.E., D.M.(Oxon.), F.R.C.S., and J. C. Goligher, Ch.M.(Edin.), F.R.C.S.(Edin., and Eng.). Vol. II. The Central Nervous System; the Eye, Ear, Nose and Throat; Mouth, Salivary Glands and Jaws; Neck; the Breast; the Esophagus; the Heart and Lungs. 694 pages, illustrated. $24.75. London: William Heinemann; Fair Lawn, New Jersey: Essential Books, Inc., 1957.

the aesophagus. On page 1 a quotation from Harvey Cushing: "don't let neurological surgery get too far away from general surgery," sets the tone of the approach of the entire book. All the chapters are consistent in that minor details of technique are stressed less than principles, even though techniques are indicated. There is no attempt at extensive consideration of specialty subjects, but rather for a usable volume for general consideration.

It is difficult to decide which chapters are best; all are done well. The chapter dealing with the central nervous sytem, the heart and the great blood vessels, and nose and throat are outstanding for their simplicity of presentation and illustration. The section on diseases of the breast is particularly well presented.

It is of interest to note from the section on head and neck surgery that tuberculous cervical adenitis is still not an uncommon disease. Discussion of the problems associated with this condition is presented succinctly in 7 pages. The American textbooks as a rule give but a passing mention. Quite obviously there are statements in the book that are not agreed upon, but these are not common. For instance, in the treatment of cardiospasm, the statement that Heller's operation is a very satisfactory procedure I am sure would not find general agreement in this country.

It is always of interest to attempt to determine whether the book does what its authors hope. The statement that the volume essentially is clinical and practical with such pathology as is necessary for diagnosis and treatment is surely well meant. They state that "the audiences it is intended to interest are general surgeons, registrars, postgraduate students, and those reading for their Fellowship and other higher examinations." This book accomplishes this intent in a very excellent manner. It is concise, it is well written, and it covers the subject admirably.

—*Charles G. Johnston.*

THE VOLUME *Introduction to Anesthesia*[4] contains 254 pages crammed full of information useful to anesthetists, particularly beginners in this field. It is truly an introduction to anesthesia and probably will have no peer in its field for many years to come. Only the essentials are covered in a broad and highly readable fashion, but many other important topics are not left out or passed over lightly. Complicated physiologic and pharmacologic processes are not dealt with in detail, nor are detailed reports of technique of regional blocks, which is well since the book was not intended to be a comprehensive text. A list of the useful subjects covered is as follows: preanesthetic rounds, physical status or "risk," the choice of anesthesia, elements of an anesthetic machine, the measurements of blood pressure, fundamentals of muscle relaxants, intubation of the trachea, a philosophy of anesthetic records, determination of the depth of general anesthesia, the recovery room, cardiac resuscitation, treatment of immediate postoperative pain and excitement, as well as the more common problems of anesthesiology and their fundamentals. An outstanding quality of the book is its easy readability. Although a somewhat slow reader, I was able to complete the entire book in approximately 10 to 12 hours.

The chapter on spinal anesthesia is of particular interest, especially the authors' comments on the etiology and treatment of spinal headaches and other sequelae of intrathecal anesthesia.

The reviewer does not remember ever reading a medical book as concise, as readable, and as interesting as this nor one which covered as much of the subjects in so few pages. The authors are to be complimented.

—*Richard A. Heitman.*

AS STATED BY THE AUTHOR, Maurice B. Strauss, the book *Body Water in Man*[5] is a presentation and a defense of the thesis first made by Ernest H. Starling in 1909 that "Man is provided with a distinct mechanism for the regulation of the amount as well as the composition of body fluids. Thirst and appetite under the regulation of essential nervous system and the kidneys under the influence of the circulatory, hormonal, and possibly neurogenic factors subserve this office."

The first portion of the book deals with the evolutional development of the regulation of water balance and osmotic equilibrium in the aquatic invertebrates to the point where mechanisms of water regulation and conservation of water have permitted terrestrial existence.

The stability of the "milieu interne" first recognized by Claude Bernard is a primary condition for freedom and independence of existence. This constancy in composition of the extracellular fluid throughout all classes of vertebrates is remarkable. It is determined largely by what the kidneys retain provided that thirst and appetite furnish a surplus. Kidneys cannot supply deficits. Freedom requires adequate intake as well as the overflow of excesses.

There is a detailed discussion concerning the control of thirst and the acquisition of water as well as the appetite for salt and the conservation of both salt and water and its control by the kidney and certain hormones of the neurohypophysial system. The role of hormones and the central nervous system on renal existence is thoroughly discussed. Newer aspects of renal physiology are reviewed, particularly that process which has to do with the renal excretion of water.

During the past decade, a great deal of work has been done on the antidiuretic hormone and the hypothalamic-hypophyseal system. More recently, the role of aldosterone in fluid volume control has been receiving a great deal of attention. An extensive bibliography concerning both of these hormones is reviewed.

This book is of particular interest to those students of renal physiology or for those who would like to be kept abreast of what has been learned in the past 10 years concerning the mechanisms of the regulation of the amount and composition of body fluids. Because of the abundant quotations and excerpts of a tremendous bibliography, the book is not easy to read as

[4]INTRODUCTION TO ANESTHESIA; THE PRINCIPLES OF SAFE PRACTICE. By Robert Dripps, M.D., James Eckenhoff, M.D., and Leroy Vandam, M.D. 254 pages, illustrated. $4.75. Philadelphia: W. B. Saunders, 1957.

[5]BODY WATER IN MAN; THE ACQUISITION AND MAINTENANCE OF THE BODY FLUIDS. By Maurice B. Strauss, M.D. 286 pages, 31 illustrations. $7.00. Boston: Little, Brown & Co., 1957.

a text particularly for the medical student or the practicing internist. For the student of renal physiology, however, it does summarize the vast amount of investigative work that has been done in this field during the past 10 years. —*Howard A. Lindberg.*

THE PHOTOGRAPHIC RECORDING OF PATIENTS, lesions, and techniques has become an integral part of the practice of medicine and surgery. This has been particularly true in ophthalmology where most surgical lesions are grossly visible externally. The book *A System of Ophthalmic Illustration*[6] written by the director of the Institute of Ophthalmology in London, presents in a concise fashion the organization and management of an ophthalmic photographic unit. After a brief discussion of the anatomy of the eye, the author describes the various pieces of equipment available and useful in ophthalmic photography. He then describes his techniques including those for cinematography and for such special tasks as keratography, goniophotography, and retinography. There is a fine chapter on the photography of gross specimens but only a paragraph is devoted to the photography of microscopic specimens, apparently because of space limitations.

This monograph will be useful to the ophthalmic surgeon anxious to record his preoperative and postoperative findings and is a must for anyone responsible for the activities of an ophthalmic photographic laboratory. Because of its special character it will have less appeal to the general surgeon. —*David Shoch.*

"THIS BOOK is written primarily for the resident casualty surgeon." So begins the preface to the first edition of *The Closed Treatment of Common Fractures*[7] by the prominent British surgeon, John Charnley. In this, the second edition of Mr. Charnley's book, his comments are still directed to the resident surgeon; yet, he has made clear his intent to write something more than an elementary manual for students and beginners. At a postgraduate level he attempts to justify on biologic grounds his advocacy of conservative treatment; similarly he has attempted to show how operative treatment can, in certain cases, be detrimental to the healing process.

The work is not intended to be an atlas of fractures. However, the reader will find a chapter dealing with each of the commonly encountered injuries. Of the 16 chapters, 11 are devoted to fractures of the following kinds and locations: humeral shaft, supracondylar humerus, radius and ulna, distal radius (Colles' fracture), proximal end of first metacarpal (Bennett's fracture), phalanges of fingers, per-trochanteric fracture of the femur, femoral shaft, femoral and tibial condyles, tibial shaft, and ankle bones. In each of these Charnley devotes several pages to the anatomy of the fracture, the stepwise mechanics of the closed reduction, and the details of immobilization by means of plaster or splint.

The first 5 chapters are concerned with the general principles of conservative management. Chapter 1 discusses, in simplified form, the formation of bridging callus and the differences in the healing of cancellous and cortical bone. The author's views on the importance of "compression" and "controlled collapse" to the process of union are elaborated; and the dangers of open operation—namely, inhibition of callus formation and interruption of periosteal blood supply with subsequent necrosis of bone—are stressed.

Chapter 2 describes "the soft tissue hinge" (the intact periosteum or ligament which may remain on the concave side of a fractured long bone) and the utility of this strap hinge in achieving reduction. The author places emphasis on "three point immobilization" of hinged fractures and illustrates the use of curved plasters in achieving this end. Although Charnley's point is well taken, it is the opinion of this reviewer that he regards the effectiveness of inelastic plaster as though it had the dynamic properties of spring metal.

Chapter 3 is a discussion of joint movement in conservative treatment. The essence here is what the author prefers to call the "Law of Closed Treatment, i.e., that after fracture of the shaft of a long bone, the associated joints will tolerate fixation for the duration of normal union without either permanent or significant loss of motion." Chapter 4, on the treatment of fractures without plaster of paris, points up the fallacy of thinking that all fractures require plaster immobilization and that the rate of fracture healing is somehow directly proportional to the degree of immobility.

The technique of plaster application is the subject of the fifth chapter, and the author has given an excellent presentation of the subject. In applying a cast to the fracture of both bones of the forearm Charnley eliminates the bowing effect of gravity by hanging the arm in a vertical position. He rightly stresses the importance of this maneuver. One wonders why he does not place the same emphasis on the deforming effects of gravity on the alignment of the tibial fracture, which he prefers to cast in the horizontal position. Many orthopedists might also question his condoning fracture of the intact cortex in effecting reduction of the greenstick fracture in a child. He makes no mention of the dangers of complete displacement of the bone, particularly in a forearm fracture, nor the effectiveness of spontaneous metaphyseal remodelling in angular deformities near the end of a long bone.

In favoring "closed" over "open" treatment of fractures the author has amply justified his stand on biologic grounds. Nevertheless, many orthopedists must consider the financial catastrophe which the method may impose in certain instances on patients who do not have the "advantages" of state supported hospitalization.

Charnley has succeeded in writing a stimulating monograph which should make the practicing orthopedist re-evaluate many of his indications for open operation. Also, it should teach the resident casualty surgeon many fundamentals which the senior staff negligently assumes he knows. —*C. Roger Sullivan.*

THE NEW MEDICAL TERMS that are being constantly added to our language make the work of the lexi-

[6] A SYSTEM OF OPHTHALMIC ILLUSTRATION. By Peter Hansell, M.R.C.S., F.R.P.S., F.B.P.A. 114 pages, 78 illustrations. $5.75. Springfield, Ill.: Charles C Thomas, 1956.

[7] THE CLOSED TREATMENT OF COMMON FRACTURES. By John Charnley, B.Sc., M.D., F.R.C.S. 2nd ed. 260 pages, illustrated. $10.00. Baltimore: Williams & Wilkins Co., 1957.

cographer a very important and essential contribution to medical progress. We cannot help but express our appreciation to the workers who undertake a time-consuming and arduous task which benefits student, practitioner, medical writer, and the many other individuals whose work brings them in contact with medical problems.

The new *Stedman's Medical Dictionary*[8] has "swelled wisibly," as did Sam Weller's tea drinking friend, but inevitably, in keeping pace with the changes and developments that take place so rapidly in the field of medicine. All of us who read and study are grateful for this new, authoritative, well illustrated, and up-to-date addition to our working tools.

—*Sumner L. Koch.*

A VERY SCHOLARLY WORK, *Anatomies of Pain*,[9] reviews man's theories about pain from ancient times to the present. The author justifies his really monumental effort by this analogy: "just as the correct appraisal of a patient is dependent upon a good clinical history, so the proper understanding of a subject such as pain requires an insight into what has been thought about it in the past."

The author first analyzes the concepts of pain held by the ancients, and then shows how these first ideas were modified and supplanted by new ones as man's knowledge of anatomy and physiology increased. Finally, a summary of our present schemas of pain pathways and a prospectus of future research are given.

The primitive mind conceived of pain as the result of "object intrusion" whereby the causal agent—usually an evil spirit—was actually directed into the victim's body. Very early, the heart occupied a position of extreme importance in pain; it was regarded as the sensory center by the ancient Egyptians, Indians, and Chinese. The lowly status of the brain was clearly shown by the Egyptians' embalming procedure whereby the brain was the only organ thrown away as waste. The Greeks were especially interested in the nature of sensory data and sense organs. Although Democritus, Plato, and others suggested that the brain was the center for sensation, Aristotle denied this idea; he constructed a cardiovascular anatomy of sensation, and thus delayed the establishment of the sensory function of the central nervous system. The influence of this authority was felt strongly down through the years even though newer and sounder concepts had appeared.

The author analyzes the developments which have occurred from the renaissance to the nineteenth century. New, sometimes bizarre, "anatomies of pain" were evolved. Anatomic investigation of the nervous system resulted in such discoveries as the anterior and posterior spinal nerves, the optic thalamus, the basal nuclei, and the cerebral cortex. Through it all the basic search for the sensorium commune persisted. There was a trend throughout the whole period toward a gradual abolition of the animal spirits as underlying motor and sensory impulses in favor of a physical interpretation of nerve function.

There is a thorough study of the contributions of such men as Albertus Magnus, Leonardo da Vinci, Vesalius, Varolio, Jean Fernel, William Harvey, van Helmont, Descartes, Spinoza, Hobbes, Thomas Willis, Borelli, Malpighi, Huygens, Newton, and others. The author's appraisal of all of these men is well documented.

During the first part of the nineteenth century, the functions of the spinal nerve roots were at last discovered (Bell-Magendie law), and within a century the spinothalamic tract and other sensory and motor patterns in the nervous system were largely mapped out.

Twentieth century studies on pain have been concerned with types of nerve endings which subserve pain, types of noxious stimuli causing pain, the essential nature of the action current underlying a nerve impulse, the nature of visceral pain, and so forth. Among the recent and contemporary researchers on pain whose contributions are reviewed in this book are the following: Leriche, Sir Thomas Lewis, Lorente de No, Penfield, Magoun, Fulton, and Wolff, to enumerate a few.

A statement of present day areas of concentration concerning pain is best given in the author's own words: "Amidst the rich diversity of suggested anatomies of pain of the twentieth century, three trends stand out—the emergence of a second sensory nervous system concerned with its conduction; the growing tendency to centralize the sensorium within the brain; and an increasing appreciation of the biochemical aspects of sensation. It is in the conviction that a reinterpretation of the old ideas in terms of new knowledge constitutes a fruitful form of scientific thought that the attempt to tell the story of the anatomies of pain has been made." In the opinion of this reviewer, the author has succeeded very well.

—*Margaret Phillips.*

THE BRIEF TREATISE of 66 pages by Nice, Margulis, and Rigler[10] covers all of the tumors of the abdomen in children. It is primarily concerned with diagnosis by means of various available types of roentgenologic examinations such as barium studies, urography, and retroperitoneal air injection. The subject matter is divided into masses in the region of the liver, other intraperitoneal masses, renal and adrenal masses, and other extraperitoneal masses.

Description of each disease entity and the illustrations are well correlated for clear understanding, and an adequate bibliography is included.

—*Harvey White.*

THE AUTHORS have emphasized in the introduction of *Nursing Care of the Surgical Patient*[11] that the sixth

[8] STEDMAN'S MEDICAL DICTIONARY. 19th rev. ed. Edited by Norman Burke Taylor, V.D., M.D., F.R.S.C., F.R.C.S. In collaboration with Lieut. Col. Allen Ellsworth Taylor, D.S.O., M.A. 1656 pages, illustrated. $12.50. Baltimore: Williams & Wilkins Co., 1957.

[9] ANATOMIES OF PAIN. By K. D. Keele, M.D., F.R.C.P. 206 pages, illustrated. $5.50. Springfield, Ill.: Charles C Thomas, 1957.

[10] ROENTGEN DIAGNOSIS OF ABDOMINAL TUMORS IN CHILDHOOD. By Charles M. Nice, Jr., M.D., Ph. D., Alexander R. Margulis, M.D., and Leo G. Rigler, M.D. 75 pages, illustrated. $4.00. Springfield, Ill.: Charles C Thomas, 1957.

[11] NURSING CARE OF THE SURGICAL PATIENT. 6th ed. By John Pettit West, M.D., Manelva Wylie Keller, B.S., R.N., and Elizabeth H. Harmon, M.A., R.N. 669 pages, illustrated. $5.75 New York: The Macmillan Co., 1957.

edition is to be used only as a guide for the beginning student. With the study questions and the up-to-date supplementary references at the close of each chapter, the instructor will have considerable latitude in assigning further material to meet the needs of individuals or groups of students.

The language throughout is understandable. The diagrams are basic, requiring more investigation on the part of the student; however, the diagram on the 3 bottle chest drainage system deserves more explanation.

The discussion covering "Surgical Treatment and Nursing Care" is consistent in plan. The stress is on teaching general principles in the care of the common conditions, as well as to provide direction concerning adequate nursing care in more complicated cases. Patient teaching is included as an important part of the nursing care. —*Jane H. Crawford.*

THE 333 PAGE BOOK *Pediatric Roentgenology*[12] contains 700 superb roentgenograms and explanatory diagrams of various diseases which occur in infants and children. Although the roentgenograms are reproduced as the x-ray positive rather than the usual negative, the detail is of such fine quality that this reversal does not detract significantly from its value.

The text is minimal and consists of a brief explanation of each disease and a short clinical history. With many of the roentgenograms there are excellent explanatory diagrams which clarify further the disease illustrated.

All of the body areas are included and profusely illustrated with roentgenograms of both normal and pathologic conditions. The most thoroughly covered region is the chest, a most important area in pediatrics.

For physicians interested in pediatrics this is an excellent, illustrated reference book. No bibliography is included. —*Harvey White.*

THE INTERESTING BOOK, *The Collected Papers of Hugh Trumble*,[13] presented as it is in a spirit of humility, serves best to reiterate the old truism that the so-called specialist is a much better specialist if he has a knowledge of medicine broadened beyond his own particular and narrowed interests, Hugh Trumble is an eminent Australian neurosurgeon, but before confining his work to that specialty he was a general surgeon with extensive clinical experience, particularly in the fields of thoracic and abdominal surgery. To the reader of his papers it is apparent that he has been able successfully to combine his investigative spirit with a career of practical surgery, and to extend his mechanical ingenuity to the creation of such devices as simplified, inexpensive orthopedic appliances and an improved craniotome.

This book is made up of a collection of 28 papers, dating from 1923 to 1954; 8 additional papers are listed but not published. More than half of the book is devoted to surgery of the nervous system, the author having had a particular interest in the autonomics, in which field he did much original investigation. Of particular interest is his report on the successful reinnervation of the paralyzed urinary bladder in dogs. His series of intracranial lesions is not as large as many of those currently appearing in the neurosurgical literature, but his results are none the less impressively good. He has always operated hopefully upon the patient with an intracranial tumor, but his attitude is one of admitting reality. He wants his patients to be more than mere "survivors."

Trumble teaches by example that which daily needs restatement in this age of gadgeteering: thoughtful attention to technical details, a sound knowledge of anatomy and physiology, and the application of careful and conscientious surgical principles will accomplish far more than reliance upon such modern props as antibiotics, blood transfusions, and expensive, more complicated instruments and appliances.

—*John Martin.*

AT THE PRESENT TIME, to the author's knowledge, *Chirurgie à coeur ouvert*[14] occupies a place which is unique in publications concerning open heart surgery. The book traces the "world-wide growth and development of the use of the two techniques currently available for operation within the open heart"; namely, hypothermia and pump-oxygenating systems. In a field which is so rapidly changing and developing, the work will soon be out-of-date, but its value will remain as a background for students of surgery interested in this field.

About one-third of this volume is devoted to tracing the experimental background and the clinical application of hypothermia for open heart surgery. The author recognizes the risks of the technique and its limitations, particularly the time limitation which is available for stopping the circulation. However, because of the safety of the method, he recommends its use for operations which can be readily done within the time limitation, namely, pulmonary valvular stenosis and atrial septal defect.

The remainder of the book is devoted to a consideration of the objectives and achievements of various instruments designed for total body circulatory bypass, as well as for right-sided and left-sided cardiac bypass. The general characteristics of an ideal system which could be used to describe the objectives of such an instrument are given. Machines developed in various countries by various investigators are thoroughly described, illustrated, and evaluated. The experimental and clinical experience up to the time of publication with each type of machine is reported. The author concludes, in general, that pump-oxygenation has achieved a stature which warrants further extensive clinical application in the hands of teams who are well-trained and experienced in this type of endeavor. He also suggests some of the immediate steps which need to be taken to achieve greater perfection

[12]PEDIATRIC ROENTGENOLOGY. By Dr. M. A. Lassrich, Prof. Dr. R. Prévôt, Prof. Dr. K. H. Schäfer. Edited by Prof. Dr. K. H. Schäfer. Translation from German by James T. Case, M.D., D.M.R.E.(Camb.). 333 pages, 700 illustrations. $28.00. New York and London: Grune & Stratton, Inc., 1957.

[13]THE COLLECTED PAPERS OF HUGH TRUMBLE. Edited by Leonard Cox, M.D., R. S. Lawson, F.R.C.S., and T. E. Lowe, M.D. Foreword by W. G. D. Upjohn, O. B. E., M.D., F.R.C.S., F.R.A.C.S. 302 pages, illustrated. Victoria, Australia: Melbourne University Press; London, New York: Cambridge University Press, 1957.

[14]CHIRURGIE À COEUR OUVERT. By Prof. Ch. Dubost and Ph. Blondeau. 320 pages, illustrated. 3.000 fr. Paris: Masson et Cie, 1957.

in such pump-oxygenators. His experience with 18 patients using pump-oxygenation is described.

In no other place, to my knowledge, is it possible to obtain as comprehensive, careful, and selective a review of the entire problem of open-heart surgery as this very easily readable profusely illustrated text in French by Dr. Dubost and Dr. Blondeau. There is a great need for an English translation of this book to be published as soon as possible. —*Henry Swan.*

THE HISTORY OF MEDICINE in the British Navy is detailed from 1200 to 1900 in two volumes, of which this review covers the first volume[15] from 1200 to 1649. It begins with the Medieval period of religious concern, progresses to the more material, acquisitive Tudor period dominated by Henry VIII and Elizabeth I, and finally to the decadent and grafting early Stuart period of James I and Charles I.

In the Medieval period, the ships served merely to transport soldiers, but later as the Navy too became a fighting service, conditions arose that increased the need for medical care at sea. But even then and for a long time to come, no doctors served aboard. The voyages were short, and not until the long voyages of exploration were undertaken were doctors really essential for the management of scurvy and tropical diseases. Many ship captains and officers engaged their own surgeons but the seaman did not benefit. The religious influence of the times accounted for the only care given to the seamen, who were landed ashore and taken into "Houses of Pity" and given reasonably good medical care. The ancient Laws of Oléron laid down all medical provisions for seamen and were followed for many centuries.

Later, when spiritualism yielded to material business and trade, the "Houses of Pity" were abolished and the lot of the sick seaman was very bad indeed. Under the Tudors, life was cheap, the Crown did nothing humanitarian, and it was up to the East India Company to initiate many medical practices which were later to be accepted by the Royal Navy. The Company was in business for a profit, most of its seamen were career men (unlike those of the Crown), and much more was done to keep the men healthy and happy on the long trading voyages. Permanent surgeons were appointed to each ship, with the authority to give medicine internally if necessary, and these men had to hand in records to the Company; thus some knowledge was acquired of the mysterious diseases that killed so many.

This authority to give medicine was the subject of a perennial conflict between physicians and surgeons, and handicapped naval medicine considerably. The surgeons, of the Barber-Surgeon guild, were not allowed for centuries to treat illness; they could treat only wounds. The physicians, however, did not go to sea, despite the predominant need for medical care. Only after centuries of struggle were surgeons legally allowed to apply medicine internally. In the meantime, thousands of seamen died, not from battle wounds but from sickness.

There is an interesting account of the Spanish Armada and of the epidemics of dysentery and typhus and food poisoning which decimated both sides—and saved the English from the powerful Armada. Death took the English seamen so fast that the ships could not be filled fast enough with pressed men; in fact, an all out battle with the Spanish would not have taken as many lives. It was a massacre of thousands on both sides with not a shot fired, and the Armada limped home with only a fraction of its complement. In time, it was agreed that physicians were needed, although with medical knowledge so rudimentary, it is doubtful that the seaman realized any immediate benefit. A great deal of progress was needed in keeping the ships clean, the food fresh, and conditions more favorable before doctors could do much good.

The heartless Tudors were followed by the equally self-centered Stuarts, James I and Charles I, whose reigns were marked by dishonesty and corruption. The last Royal Navy to be the feudal possession of an English king declined rapidly, and although Charles tried to improve the lot of the seaman, his reforms would not come about in his ill-starred reign.

"The medical service of the Navy was born of no religion, the offspring of sheer necessity."

—*C. A. Broaddus, Jr.*

THE BOOK entitled *The Anatomy of Congenital Pulmonary Stenosis*[16] by Sir Russell Brock is an important contribution in this field by one who has been most concerned with this particular aspect of congenital heart disease. The volume begins with a selection and condensation of the literature on the comparative anatomy and embryology of the right ventricular outflow tract and pulmonary artery with an eye to explaining the variants of pulmonary stenosis encountered clinically. Of more interest and importance are the subsequent chapters on the observations of the author in the cases he has seen of pulmonary stenosis, both with an intact septum (trilogy of Fallot, pure pulmonary stenosis) and with a ventricular septal defect in the tetralogy of Fallot. Particularly helpful are the classification and description of the various types of pulmonary stenosis and atresia, a particularly timely work in view of the current emphasis on the complete correction of the cardiac defects in the tetralogy of Fallot.

On the basis of his observations and ideas he develops his concept of the regulatory function of the outflow tract of the right ventricle, both in the tetralogy of Fallot and in the normal individual. The anatomic and physiologic considerations are documented with pressure tracings taken at the time of operative attack upon the defect and photographs of post-mortem specimens. One might expect the bibliography of a monograph to be more complete than the list of references given, especially in regard to some of the American contributions, but perhaps this is excusable since the book represents largely a compilation of the author's own observations. This is an

[15]MEDICINE AND THE NAVY 1200-1900. By J. J. Keevil. Introduction by Sir Henry Dale. Vol. I—1200-1649. 255 pages, illustrated. $8.50. Edinburgh and London: E. & S. Livingstone, Ltd., Baltimore: Williams & Wilkins Co., 1957.

[16]THE ANATOMY OF CONGENITAL PULMONARY STENOSIS. By Sir Russell Brock, M.D., F.R.C.S., F.A.C.S. 114 pages, 77 illustrations. $7.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1957.

important contribution to the subject, although probably not as uniquely outstanding as the author's earlier book, *Lung Abscess.* —*Henry T. Bahnson.*

THE SMALL VOLUME entitled *The Healing of Wounds,*[17] edited by Martin B. Williamson, is an excellent presentation of certain fundamental and theoretic aspects of wound healing. It is composed of 10 sections written by 12 contributors, representing different but allied fields. These contributors have reviewed a vast amount of accumulated material and present this basic information in a condensed form. At the end of each section there is a very useful bibliography.

Sections 1 through 4 deal with the metabolism of proteins, amino acids, the role of ground substances and sulfur compounds. Sections 5 and 6 are devoted to vitamin C and hormonal influence.

Section 10 is a review of the clinical approaches to the concepts of wound healing. Here again, one is reminded of the importance of Osler's principle, "To do no harm," and of the accuracy of the observation that wound healing is a function of living tissue which is not hastened or stimulated, but often retarded by any chemical agent applied to the surface.

—*Russell T. Bothe.*

[17]THE HEALING OF WOUNDS: A SYMPOSIUM ON RECENT TRENDS AND STUDIES. Edited by Martin B. Williamson, Ph.D. 202 pages, illustrated. $7.00. New York: McGraw-Hill Book Co., Inc., 1957.

BOOKS RECEIVED

BOOKS received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

ANATOMY AND PHYSIOLOGY FOR NURSES. By W. P. Gowland, M.D. (Lond.), F.R.C.S. (Eng.), and John Cairney, D.Sc., M.D., F.R.A.C.S. 5th ed. 536 pages, 204 illustrations. 45/-. New Zealand: N. M. Peryer Ltd., 1958.

BIBLIOGRAPHY OF INTERNATIONAL CONGRESSES OF MEDICAL SCIENCES. Prepared by W. J. Bishop under the auspices of the Council for International Organizations of Medical Sciences. 238 pages. $5.50. Springfield, Ill.: Charles C Thomas, 1958.

HOMOSEXUALITY TRANSVESTISM AND CHANGE OF SEX. By Eugene de Savitsch, M.D. 120 pages, 6 illustrations. $3.50. Springfield, Ill.: Charles C Thomas, 1958.

THE ESOPHAGUS; MEDICAL AND SURGICAL MANAGEMENT. By Edward B. Benedict, M.D., F.A.C.S., and George L. Nardi, M.D., F.A.C.S. Foreword by Edward D. Churchill, M.D., F.A.C.S. 390 pages, 108 illustrations, 16 color plates. $15.00. Boston: Little, Brown & Co., 1958.

SIMPLE METHODS OF CONTRACEPTION; AN ASSESSMENT OF THEIR MEDICAL, MORAL AND SOCIAL IMPLICATIONS. Edited by Winfield Best and Frederick S. Jaffe. Foreword by R. Gordon Douglas, M.D. 63 pages. New York: Planned Parenthood Federation of America, 1958.

HUMAN DISSECTION; ITS DRAMA AND STRUGGLE. By A. M. Lassek, M.D., Ph.D. 310 pages, 15 illustrations. $6.50. Springfield, Ill.: Charles C Thomas, 1958.

BLOOD GROUPS IN MAN. By R. R. Race, Ph.D., M.R.C.S., F.R.S., and Ruth Sanger, Ph.D., B.Sc. Foreword by Professor Sir Ronald Fisher, F.R.S. 3rd ed. 377 pages, 31 illustrations. $8.50. Springfield, Ill.: Charles C Thomas, 1958.

THE PRACTICE OF NUCLEAR MEDICINE. By William H. Blahd, M.D., Franz K. Bauer, M.D., and Benedict Cassen, Ph.D. Introduction by Paul Aebersold, Ph.D. Foreword by Joseph F. Ross, M.D. 407 pages, 111 illustrations. $12.50. Springfield, Ill.: Charles C Thomas, 1958.

BIBLIOTHECA GYNAECOLOGICA, SUPPLEMENTUM AD GYNAECOLOGIA. Fasc. 18. FORTSCHRITTE DER GEBURTSCHILFE UND GYNAKOLOGIE. Edited by A. Reist, Zurich. Vol. VIII. PRAE-UND POSTOPERATIVE BEHANDLUNG BEI GYNAEKOLOGISCHEN OPERATIONEN. By F. Kern. 75 pages, illustrated. Basel and New York: S. Karger, 1958.

CONGENITAL ANOMALIES OF THE HAND AND THEIR SURGICAL TREATMENT. By Arthur Joseph Barsky, M.D., D.D.S. 165 pages, 77 illustrations. $5.75. Springfield, Ill.: Charles C Thomas, 1958.

DISINFECTANTS; THEIR VALUES AND USES. By W. E. Finch. 188 pages, 14 illustrations. $5.50. New York: The Macmillan Co., 1958.

SIR CHARLES BELL; HIS LIFE AND TIMES. By Sir Gordon Gordon-Taylor, K.B.E., C.B., F.R.C.S., and E. W. Walls, M.D., Ch.B., B.Sc., F.R.S.(Ed.). 288 pages, 49 illustrations. $8.50. Baltimore: The Williams & Wilkins Co., 1958; Edinburgh and London: E. & S. Livingstone Ltd., 1958.

RIUNIONI MEDICO-CHIRURGICHE INTERNAZIONALI. RIUNIONE DE OSTETRICIA E GINECOLOGIA. ATTI DEL SIMPOSIO SULLA TERAPIA DEL CANCRO DELL'UTERO. Presidente del Simposio—Prof. A. Brunschwig. 435 pages, illustrated. L 5000. Saluzzo, Italy: Edizioni Minerva Medical, 1957.

A SYNOPSIS OF SURGICAL ANATOMY. By Alexander Lee McGregor, M.Ch.(Edin.), F.R.C.S.(Eng.). Foreword by Sir Harold J. Stiles, K.B.E., F.R.C.S.(Edin.). 8th ed. 808 pages, 766 illustrations. $7.00. Baltimore: The Williams & Wilkins Co., 1957.

KLINISCHE ENZYMOLOGIE; DIE FERMENTE IN DER PATHOGENESE DIAGNOSTIK UND THERAPIE. By Dr. Med. Rudolf Abderhalden. 371 pages, 34 illustrations. Stuttgart: Georg Thieme Verlag, 1958.

OPERATIVE SURGERY. Edited by Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Vol. VIII. Neurosurgery; Eyes, Ear, Nose and Throat. 196 pages, illustrated. London: Butterworth & Co. (Publishers) Ltd., 1958. (Distributed by F. A. Davis Co.)

THE AUTHOR PUBLISHER PRINTER COMPLEX. By Robert S. Gill. 3rd ed. 134 pages, 8 illustrations. $2.25. Baltimore: The Williams & Wilkins Co., 1958.

AN INTRODUCTION TO SURGERY. Edited by David H. Patey, M.S.(Lond.), F.R.C.S.(Eng.). 228 pages, 54 illustrations. $3.00. Chicago: The Year Book Publishers, Inc., 1958.